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Potential Drug-Drug Interaction (DDI) in Type 2 Diabetes Mellitus Outpatients in Palembang: a Retrospective Study

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ABSTRACT

This study aimed to identify and describe potential drug–drug interactions (DDIs) among outpatients with type 2 diabetes mellitus (T2DM) at Hospital X (Palembang, Indonesia) by analysing patient characteristics, patterns of antidiabetic drug use, comorbidities, concomitant medications, and the severity of potential interactions. A descriptive retrospective design was applied using secondary data from outpatient medical records during January–December 2024. From a total of 1,486 records, 316 eligible records were included based on predefined inclusion criteria, with the minimum sample size determined using Slovin's formula. Potential DDI severity was categorised into major, moderate, and minor. Most patients were female (66.13%) and aged ≥60 years (51.58%). Metformin was the most frequently prescribed antidiabetic drug (25.38%), followed by insulin Apidra (15.45%), insulin Sansulin (14.12%), and glimepiride (12.78%). Potential DDIs were identified in 255 patients (80.69%); across 649 interaction events, most were moderate (93.52%), followed by minor (5.72%) and major (0.75%). The remaining 61 patients (19.31%) had no potential DDIs. Overall, the high utilisation of multi-drug regimens in outpatient T2DM care is associated with substantial exposure to potential DDIs, predominantly of moderate severity, underscoring the need for routine medication review and therapeutic monitoring to improve medication safety, with clinical pharmacists playing an important role in supporting prescribers.

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ABSTRAK

Penelitian ini bertujuan untuk mengidentifikasi dan mendeskripsikan potensi interaksi obat–obat (drug–drug interactions/DDIs) pada pasien rawat jalan diabetes melitus tipe 2 (DMT2) di Hospital X (Palembang, Indonesia) melalui analisis karakteristik pasien, pola penggunaan obat antidiabetik, komorbiditas, penggunaan obat penyerta, serta tingkat keparahan potensi interaksi. Penelitian deskriptif dengan desain retrospektif ini menggunakan data sekunder rekam medis rawat jalan periode Januari–Desember 2024. Dari total 1.486 rekam medis, sebanyak 316 rekam medis yang memenuhi kriteria inklusi dianalisis, dengan besar sampel minimum ditentukan menggunakan rumus Slovin. Tingkat keparahan potensi DDI diklasifikasikan menjadi major, moderate, dan minor. Mayoritas pasien berjenis kelamin perempuan (66,13%) dan berusia ≥60 tahun (51,58%). Obat antidiabetik yang paling sering diresepkan adalah metformin (25,38%), diikuti insulin Apidra (15,45%), insulin Sansulin (14,12%), dan glimepiride (12,78%). Potensi DDI ditemukan pada 255 pasien (80,69%); dari total 649 kejadian interaksi, sebagian besar termasuk moderate (93,52%), diikuti minor (5,72%) dan major (0,75%). Sebanyak 61 pasien (19,31%) tidak memiliki potensi DDI. Secara keseluruhan, tingginya penggunaan regimen multiobat pada pelayanan rawat jalan DMT2 berkaitan dengan paparan potensi DDI yang cukup besar, terutama interaksi derajat moderate, sehingga diperlukan review obat dan monitoring terapi secara rutin untuk meningkatkan keselamatan pengobatan, dengan dukungan peran farmasis klinik dalam membantu prescriber melakukan evaluasi interaksi dan optimasi terapi.

Kata Kunci: Diabetes melitus tipe 2; Potensi interaksi obat–obat; Penggunaan obat antidiabetik; Polifarmasi; Pelayanan rawat jalan

Diabetes mellitus tipe 2; interaksi obat;obat antidiabetes; perawatan rawat jalan

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or a combination of both, and it is associated with progressive microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease. Clinically, DM is commonly categorised into type 1 diabetes, which typically requires lifelong insulin replacement, and type 2 diabetes mellitus (T2DM), which is primarily driven by insulin resistance and is managed through lifestyle modification and pharmacotherapy that may include oral agents and or insulin depending on disease severity and response to treatment. Pharmacological management of T2DM encompasses several therapeutic classes, such as insulin secretagogues, biguanides, insulin sensitizers, alpha-glucosidase inhibitors, incretin-based therapies, and SGLT2 inhibitors. In practice, combination therapy is frequently initiated or escalated when monotherapy fails to achieve adequate glycaemic control, particularly in patients with longer disease duration and multiple comorbidities [1].

The pathogenesis of T2DM is multifactorial and reflects the interplay between peripheral insulin resistance and progressive pancreatic β-cell dysfunction. Insulin resistance in skeletal muscle and adipose tissue reduces glucose uptake, whereas hepatic insulin resistance promotes increased gluconeogenesis and endogenous glucose production; concurrently, β-cell dysfunction limits compensatory insulin secretion. Chronic hyperglycaemia is further reinforced by lipotoxicity, oxidative stress, and low-grade systemic inflammation, which collectively accelerate β-cell exhaustion and contribute to the development of diabetic complications. As a result, patients with T2DM

are prone to both microvascular outcomes, such as retinopathy, nephropathy, and neuropathy, and macrovascular events, including coronary artery disease and stroke [2].

Over recent decades, the burden of T2DM has risen substantially worldwide. The World Health Organization (WHO) has articulated a global commitment to halting the rise in diabetes and obesity as part of international targets [2]. Consistently, the International Diabetes Federation (IDF) reported that 537 million people were living with diabetes globally in 2021, with projections increasing to 643 million by 2030 and 783 million by 2045. Indonesia ranks among the countries with the highest number of diabetes cases, with an estimated 19.5 million cases in 2021 and a projected increase to 28.6 million by 2045 [3]. Among adults aged 20–79 years, the prevalence of diabetes has been reported as 10.6% (approximately 1 in 9 individuals), accompanied by substantial diabetes-related mortality and a large proportion of undiagnosed cases [3]. At the regional level, South Sumatra has shown a marked increase in reported diabetes cases from 279,345 in 2021 to 434,461 in 2022, with Palembang reported as having the highest prevalence within the province [4].

The long-term management of T2DM frequently involves multiple medications to control hyperglycaemia and address comorbidities such as hypertension, dyslipidaemia, and cardiovascular disease, thereby increasing the likelihood of drug-related problems (DRPs). DRPs are defined as drug therapy–related events that may interfere with expected clinical outcomes [5], and drug interactions represent one of the most frequently encountered DRPs in practice [6]. Drug interactions arise when two or more substances influence each other's pharmacological effects, altering efficacy and/or toxicity [7]. Such interactions may involve drugs, foods, beverages, or other concomitantly administered chemicals [8]. Interactions become clinically relevant when they increase toxicity, reduce therapeutic effectiveness, or compromise safety—particularly for agents with narrow therapeutic indices or in vulnerable populations such as older adults and patients receiving polypharmacy [9]. In routine clinical practice, drug interactions are often categorised by severity into minor, moderate, and major interactions, with major interactions considered potentially life-threatening and typically requiring close monitoring or therapeutic modification [10].

Previous studies in Indonesian settings have indicated that patients with T2DM are frequently exposed to potential drug–drug interactions. Among 46 hospitalised patients with T2DM at Gunung Maria Hospital, Tomohon, 32 patients (69.57%) were reported to be at risk of drug interactions, with 55 interaction events identified; pharmacodynamic interactions predominated, and severity ranged from major to minor categories [11]. Similarly, an analysis of 250 prescriptions at Pharmacy X in Jambi identified 48 potential DDI cases, with moderate interactions constituting the largest proportion, followed by minor and major categories [11]. These findings collectively suggest that potential DDIs are common across different care settings, yet patterns of antidiabetic use, comorbidity profiles, and concomitant medications may generate distinct interaction risks in each local context.

Based on this background, the present study was conducted to evaluate antidiabetic drug utilisation and potential drug–drug interactions among T2DM outpatients at Hospital X (Palembang, Indonesia) during 2024. The findings are expected to support safer prescribing, strengthen medication monitoring practices, and contribute to improving pharmaceutical care services by reducing preventable interaction-related risks and enhancing the quality of patient management.

2. Method

Study Design and Study Period

This descriptive retrospective study analysed outpatient medical records from January to December 2024. Data retrieval, extraction, and verification from the Hospital X medical record system were performed during April–May 2025.

Study Population and Sample Size

The study population consisted of all outpatient medical records of patients diagnosed with type 2 diabetes mellitus (T2DM) who received antidiabetic drug therapy during the study period. From a total of 1,486 medical records, the minimum sample size was determined as 316 records using Slovin's formula.

Inclusion Criteria

Medical records were included if they met all of the following criteria: (1) patients aged >18 years; (2) clear and complete medical record documentation; (3) documented use of antidiabetic therapy, either oral agents and/or insulin; and (4) receiving at least two antidiabetic drugs, with or without comorbidities.

Exclusion Criteria

Medical records were excluded if they did not meet the inclusion criteria, particularly if key information required for medication profiling and interaction assessment was incomplete or unclear (e.g., missing drug names, dose, frequency, or incomplete concomitant medication list), if the record did not represent a T2DM outpatient case within the defined study period, or if the antidiabetic regimen involved fewer than two antidiabetic drugs.

Data Collection and Study Variables

Data were collected retrospectively by reviewing medical records that met the inclusion criteria. Extracted information included patient characteristics, diagnoses and comorbidities, antidiabetic drug regimens, concomitant medications (non-antidiabetic drugs), and potential drug–drug interactions (DDIs). Data extraction was conducted using a structured recording sheet, and the dataset was compiled and processed using Microsoft Excel.

Identification of Potential Drug–Drug Interactions and Severity Classification

Potential DDIs were identified using Drugs.com, Medscape, Stockley's Drug Interactions, and relevant scientific journals [11]. Potential DDIs were defined as drug pairs co-administered within the same regimen that were flagged by the screening sources as having interaction potential. Interaction severity was reported according to the categories provided by the screening references (e.g., major, moderate, and minor).

Data Analysis

Data were analysed descriptively to summarise patient characteristics, patterns of antidiabetic drug use, comorbidities, use of non-antidiabetic drugs, potential DDIs, and the severity distribution of interactions. Results were presented in tables and narrative form to facilitate interpretation.

Ethical Considerations

This study has been reviewed and approved by the Ethics Committee of the General Hospital of Palembang BARI (RSUD Palembang BARI) under approval number: 420/0206/RSUD/2025. Patient confidentiality was strictly maintained through the use of anonymized data and by limiting the analysis to only the necessary variables for the study. All ethical standards regarding patient privacy and data protection were adhered to in compliance with the relevant guidelines throughout the process.

3. Results and Discussion

Patient Characteristics

A total of 316 outpatient medical records of patients with type 2 diabetes mellitus (T2DM) were analysed. The cohort was predominantly female (209; 66.13%) compared with males (107; 33.86%). In terms of age, elderly patients (≥60 years) constituted a slightly larger proportion of the study population (163; 51.58%) than adults aged 19–59 years (153; 48.41%) (**Table 1**). This demographic pattern is consistent with earlier reports indicating a higher proportion of female T2DM patients in clinical settings [12], [13], and it may be partially explained by physiological and hormonal determinants such as higher adiposity and postmenopausal endocrine changes that are associated with increased insulin resistance [14], [15]. The predominance of older patients is also biologically plausible, given that ageing is accompanied by progressive decline in β-cell function, impaired glucose tolerance, and reduced insulin sensitivity, thereby increasing vulnerability to T2DM and its complications [16].

Table 1. Patient Characteristics (n = 316)

Characteristic	Category	n	%
Gender	Male	107	33.86
	Female	209	66.13
Age	19–59 years	153	48.41
	≥60 years	163	51.58

Pattern of Antidiabetic Drug Use

The utilisation profile of antidiabetic therapy is presented in **Table 2**. Metformin was the most frequently prescribed antidiabetic agent (132; 25.38%), followed by insulin glulisine (Apidra) (78; 15.45%), regular insulin (Sansulin) (72; 14.12%), and glimepiride (66; 12.78%). Overall, the distribution indicates that both oral antidiabetic drugs and multiple insulin preparations were commonly used in this outpatient cohort, suggesting a population requiring combination regimens and, in a substantial proportion, insulin-based glycaemic control.

Table 2. Pattern of Antidiabetic Drug Use (n = 316)

Antidiabetic drug	n	%
Metformin	132	25.38
Insulin Apidra	78	15.45
Insulin Sansulin	72	14.12
Glimepiride	66	12.78
Acarbose	41	7.94
Insulin Lantus	39	7.50
Insulin Novorapid	34	6.59
Pioglitazone	17	3.29
Insulin Novomix	12	2.32
Insulin Humalog	11	2.11
Insulin Levemir	10	1.92
Vildagliptin	9	1.73
Empagliflozin	8	1.53
Linagliptin	6	1.15
Glibenclamide	5	0.96
Gliclazide	4	0.77

The predominance of metformin is clinically coherent with current recommendations positioning metformin as first-line pharmacotherapy for T2DM, given its effectiveness, safety profile, and established role in reducing hepatic gluconeogenesis while improving peripheral insulin sensitivity. PERKENI (2019) similarly recommends metformin as the foundational agent for most patients with T2DM, particularly at the initiation of pharmacological therapy [17]. The relatively high frequency of insulin use (Apidra, Sansulin, Lantus, NovoRapid, NovoMix, Humalog, and Levemir) likely reflects clinical complexity, including inadequate glycaemic control with oral agents alone, longer disease duration, or the presence of complications and comorbidities requiring tighter glycaemic targets. Comparable patterns—where metformin remains dominant yet insulin use is substantial in more complex cases—have also been reported in prior studies [17].

Comorbidity Profile in T2DM Outpatients

The comorbidity profile of the outpatient T2DM cohort is summarised in **Table 3**. Cardiovascular-related conditions were predominant, with hypertensive heart disease representing the most frequently documented comorbidity (149; 26.90%), followed by coronary artery disease (100; 18.08%) and hypertension (95; 17.17%). In addition, a considerable proportion of patients presented with chronic kidney disease (84; 15.21%) and dyslipidaemia (70; 12.68%), while heart failure, stroke, and asthma were recorded at lower frequencies.

Table 3. Comorbidities Among the Patients

Comorbidity/Diagnosis	n	%
Hypertensive Heart Disease	149	26.90
Coronary Artery Disease	100	18.08
Hypertension	95	17.17
Chronic Kidney Disease	84	15.21
Dyslipidemia	70	12.68
Heart Failure	43	7.80
Stroke	23	4.15
Asthma	12	2.16

This pattern reinforces the well-established clustering of T2DM with cardiometabolic disorders and end-organ complications. Hypertension, in particular, has been described as a condition that may aggravate insulin resistance and accelerate vascular complications in patients with T2DM [17]. Contemporary prevention frameworks for cardiovascular disease also emphasise that uncontrolled blood pressure is a central driver of coronary artery disease and related atherosclerotic outcomes [18],[19]. The presence of chronic kidney disease and dyslipidaemia further signals a clinically complex population, in which polypharmacy is frequently unavoidable; consequently, the probability of potential drug–drug interactions increases in parallel with comorbidity burden and regimen complexity.

Concomitant Non-Antidiabetic Medications

The utilisation of non-antidiabetic medications during outpatient therapy is presented in **Table 4**. The most commonly prescribed concomitant drug was amlodipine (144; 10.42%), followed by candesartan (69; 4.99%) and aspirin (68; 4.92%). Other frequently recorded agents included bisoprolol (61; 4.41%), atorvastatin (59; 4.27%), clopidogrel (56; 4.05%), and diuretics such as furosemide (54; 3.91%) and spironolactone (52; 3.76%), as well as simvastatin (50; 3.62%). Collectively, this medication profile reflects the substantial cardiovascular and renal comorbidity burden observed in this

cohort (**Table 3**) and indicates that polypharmacy is a dominant feature of outpatient management in T2DM.

Table 4. Use of Non-Antidiabetic Drugs in Outpatients

Drug	n	%
Amlodipine	144	10.42
Candesartan	69	4.99
Aspirin	68	4.92
Bisoprolol	61	4.41
Atorvastatin	59	4.27
Clopidogrel	56	4.05
Furosemide	54	3.91
Spironolactone	52	3.76
Simvastatin	50	3.62
Other drugs	748	54.65

From a clinical perspective, the predominance of antihypertensive agents (amlodipine and candesartan) is coherent with guideline-based management of blood pressure in high-risk populations. The JNC VIII recommendations position calcium-channel blockers and angiotensin receptor blockers among the preferred agents for hypertension therapy, particularly in patients with cardiometabolic risk and end-organ vulnerability [20]. Likewise, the frequent use of antiplatelet therapy (aspirin and clopidogrel) is consistent with cardiovascular risk reduction strategies in patients with established atherosclerotic disease or high-risk profiles [21]. The concurrent high use of statins further supports a preventive strategy addressing dyslipidaemia and global cardiovascular risk, although the combined presence of multiple cardiometabolic agents also increases the likelihood of potential pharmacodynamic and pharmacokinetic interactions that require structured monitoring.

Prevalence and Severity of Potential DDIs

Potential drug–drug interactions (DDIs) were identified in 255 of 316 patients (80.69%), indicating that most outpatients with T2DM were exposed to at least one potentially interacting drug combination during therapy. In total, 649 potential DDI events were recorded. Regarding severity, the interaction events were predominantly classified as moderate (607; 93.52%), while minor interactions accounted for 37 events (5.72%) and major interactions were relatively infrequent (5 events; 0.75%) (Table 5). This distribution suggests that, although severe interactions were uncommon, the overall interaction burden was substantial and largely composed of moderate events that remain clinically meaningful because they may still require monitoring, dose adjustment, or therapy optimisation.

The predominance of moderate interactions is consistent with previous reports in comparable patient populations, where advanced age, multiple comorbidities, and polypharmacy collectively increase exposure to potential DDIs, yet most flagged interactions fall into the moderate category rather than immediate high-risk events [10], [11]. In practical terms, these findings highlight that outpatient medication safety initiatives should prioritise routine screening and targeted monitoring for moderate interactions, particularly those affecting glycaemic control, to prevent avoidable adverse events and loss of therapeutic stability.

Table 5. Prevalence and Severity of Potential Drug–Drug Interactions (DDIs)

Domain	Category	n	%
Patient-level prevalence (n = 316)	Patients with ≥1 potential DDI	255	80.69
	Patients with no potential DDI	61	19.31
Event-level severity (total events = 649)	Moderate	607	93.52
	Minor	37	5.72
	Major	5	0.75
	Total	649	100.00

Clinically Relevant Interaction Patterns

Beyond the overall prevalence and severity distribution, the clinically meaningful value of potential DDI screening lies in recognising interaction patterns that can destabilise glycaemic control and precipitate preventable adverse events. In this cohort, the most relevant potential interactions clustered around combinations of insulin and/or sulfonylureas with commonly co-prescribed agents for infections and cardiovascular prevention. The key interaction pairs and their clinical impacts are summarised in **Table 6**.

Several interaction pairs identified in this study primarily pose a risk of hypoglycaemia or impaired recognition of hypoglycaemic episodes. The concomitant use of sulfonylureas/insulin with quinolones may disrupt glucose homeostasis, producing either hypoglycaemia or hyperglycaemia, with older adults considered particularly vulnerable [22]. Similarly, insulin combined with antiplatelet agents may enhance the hypoglycaemic effect [23], while sulfonylureas combined with aspirin may increase the free fraction of glimepiride, potentially intensifying glucose-lowering effects [24]. The co-administration of insulin with β-blockers is also clinically important because β-blockers can prolong hypoglycaemia and may mask adrenergic warning symptoms, delaying recognition and timely correction [25]. In addition, interactions involving insulin with ACE inhibitors [26], fenofibrate [28], and NSAIDs [30] may further increase susceptibility to hypoglycaemia or amplify glucose-lowering effects, thereby necessitating closer monitoring.

In contrast, a smaller subset of interactions may contribute to loss of glycaemic control and risk of hyperglycaemia. Notably, insulin used together with corticosteroids is associated with increased blood glucose levels, which may require anticipatory dose adjustment and intensified monitoring to maintain therapeutic targets [29]. Interactions involving clonidine may also alter glycaemic control [27], reinforcing that interaction effects can be bidirectional and context-dependent, particularly in patients receiving multiple agents that affect autonomic tone or metabolic homeostasis. Overall, as summarised in **Table 6**, these interaction patterns highlight the need for systematic screening and proactive monitoring strategies in outpatient practice.

Table 6. Clinically Relevant Potential Drug–Drug Interaction (DDI) Patterns and Clinical Impact

Interaction pair	Clinical impact (primary concern)	References
Sulfonylurea/Insulin + Quinolones	Risk of impaired glucose homeostasis	[22]
Insulin + Antiplatelet agents	Increased hypoglycaemic effect	[23]
Sulfonylurea + Aspirin	Increased free fraction of glimepiride	[24]
Insulin + β-blockers	Prolonged hypoglycaemia and potential masking of symptoms	[25]
Insulin + ACE inhibitors	Risk of enhanced hypoglycaemia	[26]
Insulin + Clonidine	Altered glycaemic control	[27]
Insulin + Fenofibrate	Risk of hypoglycaemia	[28]
Insulin + Corticosteroids	Increased blood glucose levels	[29]
Insulin + NSAIDs	Enhanced hypoglycaemic effect	[30]

Pharmaceutical Care and Patient Safety Implications

The high prevalence of potential DDIs in this outpatient cohort, coupled with the dominance of moderate-severity events, highlights a pragmatic patient-safety gap that is often underestimated in routine chronic disease care. Although most interactions were not categorised as major, moderate interactions remain clinically consequential because they can lead to destabilised glycaemic control, delayed recognition of hypoglycaemia, or avoidable fluctuations in therapeutic response when monitoring and follow-up are not optimally implemented. In this context, structured pharmaceutical care becomes central to risk mitigation, particularly in older adults with cardiometabolic comorbidities who are exposed to multi-drug regimens.

A feasible safety strategy is the routine integration of medication review at key points of care, including prescription dispensing and follow-up visits. Such review should prioritise identification of high-risk interaction clusters that were prominent in this study, especially combinations of insulin and/or sulfonylureas with quinolones, antiplatelet agents, β-blockers, ACE inhibitors, NSAIDs, and corticosteroids. Practical interventions include targeted blood glucose monitoring, anticipatory counselling regarding symptoms of hypo- and hyperglycaemia, and therapy adjustment when clinically indicated. Importantly, collaboration between physicians and pharmacists is essential to translate interaction screening outputs into patient-specific decision-making, thereby preventing potential DDIs from progressing into clinically apparent adverse drug events. The strengthening of clinical pharmacy services and interprofessional communication has been consistently emphasised as a key mechanism to improve medication safety, reduce preventable harm, and optimise therapeutic outcomes in patients receiving polypharmacy [31].

Limitations of the Study

Several limitations should be considered when interpreting the findings. First, potential DDIs were identified based on interaction-screening resources and documented medication profiles, which means that the study quantified *potential* interactions rather than confirmed clinical outcomes; consequently, not all flagged DDIs necessarily translated into clinically manifested adverse events. Second, as a retrospective chart review, the analysis depended on the completeness and accuracy of medical record documentation, and unrecorded exposures such as over the counter

medicines, traditional remedies, or self-medication could not be evaluated, potentially leading to underestimation of certain interaction risks.

Third, the inclusion criterion requiring patients to receive at least two antidiabetic drugs may have increased the measured prevalence of potential DDIs by design, because combination antidiabetic therapy inherently elevates the opportunity for interaction with concomitant medications. This sampling focus is informative for assessing interaction risk in patients managed with multi-agent regimens; however, it may limit generalisability to T2DM outpatients treated with monotherapy. Finally, the study did not assess longitudinal clinical endpoints, such as documented hypoglycaemic episodes, hospitalisation, or therapy modification following interaction detection, which would be valuable to establish the clinical magnitude and outcomes of the identified potential DDIs in future research.

4. Conclusion

This study demonstrates a high burden of potential drug–drug interactions (DDIs) among outpatients with type 2 diabetes mellitus (T2DM) at Hospital X (Palembang, Indonesia), with 255 of 316 patients (80.69%) experiencing at least one potential DDI and a total of 649 interaction events identified. Most interactions were classified as moderate in severity (93.52%), indicating that, although major interactions were uncommon, clinically meaningful interaction risks remain prevalent in routine outpatient care. These findings underscore the importance of routine medication review, targeted glycaemic monitoring, and systematic interaction screening to reduce preventable medication-related harm. Strengthening the role of clinical pharmacists in collaborating with prescribers to evaluate interaction risks and optimise therapy is therefore essential to improving medication safety and the quality of patient care.

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Conflicts of Interest:
The author declares that there are no conflicts of interest in this research.

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