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Identification of Drug-Drug Interaction in Outpatient Prescription & Their Impact on Patient Safety & Healthcare Outcomes: A Retrospective Study

Rushikesh B. Takale[1], Sudheer K. Langare[2], Sushant D. Nikam[3], Yash S. Kolekar[4], Siddhesh N. Shelke[5]

[1,3,4,5]Student, [2]Assistant Professor

B. Pharmacy,

Mahadevrao Wandre Institute of Technology, Turkewadi, Kolhapur, India

Abstract :

Drug-drug interactions (DDIs) are a major concern in outpatient care, particularly among patients managing multiple chronic conditions requiring polypharmacy. This retrospective observational study was conducted to identify and assess the frequency, severity, and clinical relevance of DDIs in outpatient prescriptions. Over a period of one month, 70 prescriptions were reviewed and analysed using Micromedex software to detect and classify DDIs as major, moderate, or minor.

The study revealed a high incidence of clinically significant interactions, with the majority classified as major. Frequent DDIs involved combinations of antidiabetic, antihypertensive, and antiplatelet medications—such as metformin with glimepiride, aspirin with clopidogrel, and dapagliflozin with other glucose-lowering agents. These combinations posed risks including hypoglycaemia, bleeding, and reduced therapeutic effectiveness.

The results emphasize the importance of thorough prescription review, use of interaction-checking tools, and awareness among healthcare providers to reduce the risk of adverse drug events. Implementing preventive strategies can significantly enhance patient safety and improve therapeutic outcomes in outpatient settings.

Keywords : Drug-Drug interaction, ADR, Micromedex Assessment tool, Pharmacokinetic, Pharmacodynamic

Introduction:

In today's healthcare system, outpatient prescription medications are essential for treating both acute and chronic diseases. Their frequent usage, however, also raises the possibility of drug interactions, which may result in unanticipated problems, negative consequences, or decreased therapeutic efficacy. Modified drug absorption, metabolism, distribution, or excretion can result from drug interactions, which happen when one treatment alters the pharmacokinetics or pharmacodynamics of another. Prescription pharmaceuticals, over-the-counter medications, herbal supplements, and even food ingredients may be involved in these interactions. (Guthrie B M. B., 2010)[1]

The Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945, govern the sale of prescription drugs, including those dispensed in outpatient settings.

The outpatient department is an important part of the overall running of the hospital. It is normally integrated with the in-patient services and staffed by consultant physicians and surgeons who also attend inpatients in the wards(OPD). Many patients are examined and given treatment as outpatients before being admitted to the hospital at a later date as inpatients. When discharged, they may attend the outpatient clinic for follow-up treatment. (Kunders, 2004)[2]

Number of outpatient consultations in India FY 2021, by sector

In the financial year 2021, there were 4.3 billion outpatient consultations in the sectors of doctor consultation and pharma prescription respectively. Outpatient consultations for diagnostic test prescriptions stood at 1.5 billion in the same financial year. (Minhas, 2013)[3]

Healthcare professionals must be aware of drug interactions in order to protect patients, maximize therapeutic results, and stop preventable adverse drug reactions (ADRs). Elderly patients and those with several comorbidities who need polypharmacy are especially at risk for interactions. This problem has been made much more complex by developments in pharmacogenomics, which have shown that genetic differences might affect drug metabolism and interaction potential. (Nikolic B, 2014)[4]

The types, processes, clinical importance, and preventative measures of outpatient prescription medication interactions are examined in this study. The study intends to raise awareness and offer helpful advice for medical practitioners in reducing the dangers associated with medication interactions in outpatient settings by examining recent data and clinical guidelines. (Guthrie B M. B., 2015)[5]

In order to make a correct analysis of potential drug interactions, the prescriber must have both a general knowledge about drug interactions and specific information about the complete medication list of the patient. (Aronson, 2015)[6]

The present study was undertaken to analyse the most commonly used outpatient prescribed drug, its frequency of consumption and adverse effects.

Literature Review:

The two main categories of drug interactions are pharmacokinetic and pharmacodynamic. Drug distribution, metabolism, excretion, and absorption are all impacted by pharmacokinetic interactions. When two medications have antagonistic, synergistic, or additive effects on the body, pharmacodynamic interactions take place.

Drug-herb and food-drug interactions are also important from a therapeutic standpoint. Milk's calcium, for example, can chelate antibiotics like tetracyclines, decreasing their effectiveness. The effects of anticoagulants like warfarin can be enhanced by herbs like garlic and ginkgo.

Understanding DDIs has been expanded by pharmacogenomics, which demonstrates how genetic variations impact enzymes such as CYP450 and change drug metabolism. (Baxter, 2023)[7]

CLASSIFYING/ARRANGING DRUG INTERACTIONS :

Drug interactions can be categorised using a variety of criteria, and classifying them involves looking at them from multiple angles. It might be more prudent to state that the following are some of the various ways of organising drug interactions from various different perspectives rather than using a phrase like "classification," which is somewhat inflexible. It also goes without saying that some types or examples of medication interactions may overlap or be repeated under different headings in this article because each type utilises a different premise or criterion for classification.

By Substance Type:

- Food-Drug
- Drug-Herb
- Drug-Drug

By Location of Interaction:

- In vitro (Pharmaceutical)

- In vivo (Pharmacological)
- Pharmacokinetic
- Pharmacodynamic

By Clinical Impact:

- Clinically Desirable
- Harmful (Nonserious, Serious or Fatal)

By Manifestation:

- Clinically Significant
- Theoretical or Non-manifesting

By Predictability:

- Highly Predictable
- Predictable
- Not Predictable
- Unestablished

By Outcome:

- Treatment Failure
- Increased Pharmacologic Effect
- Toxic Reactions

Other Categories:

- Reparative Interactions
- Interactions with Unknown Mechanisms

Different types of drug-drug interactions :

1. Food-Drug Interactions
2. Drug-Herb Interactions
3. In vitro (Pharmaceutical) Drug Interactions
4. In vivo (Pharmacological) Drug Interactions
   i) Pharmacokinetic Drug Interactions
   ii) Pharmacodynamic drug interactions
5. Clinically Desirable (Beneficial) Drug Interactions
6. Serious Drug Interactions
7. Predictable Drug Interactions
8. Reparative Drug Interactions

1. Food-Drug Interactions :

In general, meals somewhat reduces the absorption of the majority of drugs. Food consumption greatly impairs the absorption and bioavailability of several medications, such as Rifampin, which is why it is recommended to take it early in the morning on an empty stomach.

Sulphonamides, fluoroquinolones, and tetracyclines chelate the calcium in milk and milk products, which reduces calcium absorption and the effectiveness of these antibiotics.

There are intriguing instances where specific food kinds improve the absorption of specific medications. Griseofulvin, saquinavir, lovastatin, and spironolactone are all more readily absorbed while eating foods high in fat. The absorption of ketoconazole is

enhanced by acidic foods, beverages, and juices. By promoting the breakdown and conversion of ferrous to ferric form, vitamin C, which is found in orange and other citrus fruits, citrus drinks, and cranberry juice, improves iron absorption. Tricyclic antidepressants are adsorbent and their absorption is decreased by a high-fiber diet. Digoxin is adsorbed by wheat bran and oatmeal, which reduces its bioavailability. (Banner Good Samaritan Medical Center, 2013) (M., 2013)[8,9]

2. **Drug-Herb Interactions :**

It is well known that several herbs may interact with warfarin, intensifying its effects. These include ginger (anticoagulant action), garlic (inhibits platelet aggregation), denshen (inhibits warfarin metabolism), and ginkgo (Gingko biloba). Omeprazole, ritonavir, and tolbutamide plasma concentrations are reduced by ginkgo. (PD., 2000)[10]

Clinical examples show that ginkgo interacts with ibuprofen, risperidone, rofecoxib, trazodone, warfarin, aspirin, diuretics, and antiepileptics. (Izzo AA, 2009)[11]

When combined with alprazolam, kava kava (Piper methysticum) is likely to cause additive central nervous system depression. (T., 2013)[12]It may also interact with levodopa and paroxetine, and it improves the clearance of CYP2E1 substrate chlorzoxazone. (Izzo AA, 2009)[11]

When combined with amantadine, an antiviral medication, cinchona bark (quinine) can cause additive CNS toxicity in the form of ataxia and mental disrientation. When combined with astemizole, an antihistamine, it can cause additive cardiotoxicity. Additionally, cinchona bark raises serum levels of carbamazepine. (Izzo AA, 2009)[11]

3. **In vitro (Pharmaceutical) Drug Interactions :**

Mixing some medications in a syringe or infusion causes them to react with one another and become inactive. Therefore, even before the drug is administered, its impact may be lost. A solution of 5% dextrose causes phenytoin to precipitate. (Quinn DI, 1997)[13]

Penicillin's, aminoglycosides, and hydrocortisone cannot be used with heparin in a syringe. Aminoglycosides and penicillins may become inactive when exposed to hydrocortisone. Sodium bicarbonate and norepinephrine cannot be combined. (Quinn DI, 1997) (KD., 2013)[13,14]

4. **In vivo (Pharmacological) Drug Interactions**

Interactions that occur inside the body are referred to be "in vivo" or "pharmacological," and this section will mostly focus on "drug-drug" interactions. These can occur when medications' pharmacokinetics or pharmacodynamics, or occasionally both, are interfered with.

i) Pharmacokinetic Drug Interactions –

Changes in the absorption, distribution, biotransformation, or elimination of one or more medications can result in pharmacokinetic drug interactions, which might have clinical ramifications as explained below. (Caterina P, 2013)[15]

- Change in pH
- Gastrointestinal motility or perfusion
- Adsorption
- Chemical reaction
- Binding
- Chelation
- First pass metabolism

ii) Pharmacodynamic drug interactions –

The dynamics of drug action are interfered with in these interactions. Drugs may interfere with one another's effects, actions, or mechanisms of action. Therefore, the main source of interference is not with kinetics but rather at the level of action, which could be a physiological system or a receptor. It can occasionally entail changing how a medicine reacts due to changes caused by compensating homeostatic reactions to drug-induced changes. (T., 2013) (JR., 2012)[12,16]

- Receptor antagonism – Competitive
- Receptor antagonism – Noncompetitive
- Physiological antagonism
- Chemical antagonism
- Physical antagonism

5. Clinically Desirable (Beneficial) Drug Interactions :

A favourable drug interaction is one in which the concurrent use of another drug either enhances a positive pharmacological effect or reduces a negative drug effect. In therapeutic practice, these medication interactions are purposefully employed or investigated to produce positive results.

Clinically desirable medication interactions include combinations like sulfadoxine-pyrimethamine or sulfamethoxazole-trimethoprim. When used in conjunction with aminoglycosides, penicillins or cephalosporins offer the advantages of two distinct modes of action. The range of activity of these combinations is frequently greater than that of the constituent parts. It is clear that a clinically desired or advantageous interaction results from the intentional use of beta lactamase inhibitors with beta lactam antibiotics. These combinations are clinically desirable: piperacillin-tazobactam, amoxicillin-clavulanic acid, and ampicillin-sulbactam. (Weber F, 2000) [17]

6. Serious Drug Interactions :

Certain negative medication interactions are regarded as severe and/or lethal. When ciprofloxacin, clarithromycin, metronidazole, cotrimoxazole, lovastatin, acetaminophen, and NSAIDs like aspirin are taken together, the exaggerated warfarin action may cause bleeding. While Rifampin is known to dramatically reduce the effect of antiepileptics, concurrent use of cimetidine, erythromycin, clarithromycin, and fluconazole is known to increase the level of antiepileptic drugs (carbamazepine, phenytoin, and phenobarbitone) and cause major toxicity. (JR., 2012) (Ament PW, 2000)[16,18]

7. Predictable Drug Interactions :

Predictable drug interactions also aid in avoiding side effects or modifying concurrent medication therapy. Tetracyclines and fluoroquinolones are less absorbed when iron is present, and vice versa. Iron also reduces the absorption of azoles, mycophenolate, and thyroxine. Antacids reduce the absorption of iron. Reduced effectiveness of different medications as a result of Rifampin, carbamazepine, and phenytoin inducing drug metabolism is predictable and useful in altering treatment plans. This information is useful when making decisions because it relates to the failure of treatment to a variety of medications, such as oral contraceptive pills, sulfonylurea hypoglycaemic agents, theophylline, cyclosporine, sirolimus, tacrolimus, diltiazem, verapamil, colchicine, beta blockers, quinidine, and oral anticoagulants.

Levodopa is less effective when used with pyridoxine and phenothiazines. Since the enzyme dopa decarboxylase is pyridoxine dependent, pyridoxine promotes the breakdown of levodopa. (JR., 2012)[16]

8. Reparative Drug Interactions :

"Reparative" refers to a particular type of pharmacological interaction. Repair is implied by the term reparative. It involves fixing a drawback or negative consequence. A reparative drug interaction occurs when two medications work together to provide a therapeutic benefit in which one medication counteracts the negative effects of the other drug. These two medications cooperate to achieve a shared positive outcome. Additionally, they counteract or compensate for one other's disadvantages because they have specific opposite effects. Both magnesium hydroxide and aluminium hydroxide have the same effect of neutralising the acid in a typical antacid combination, and this advantageous effect is added. They also have opposing effects on gastrointestinal motility at the same time. While beta blockers like propranolol cause bradycardia,

nitrates cause reflex tachycardia. Additionally, beta blockers are known to lower cardiac contractility, whereas nitrates increase it. As a result, nitrates counteract the ventricular dilatation that beta blockers cause. (Weber F, 2000)[17]

Drug-Drug Interaction Based on Severity & Possible Reaction :

1. Major Interactions (Severe - Avoid Combination)

- ❖ Ticagrelor + Aspirin (Atorvastatin & Aspirin capsule)
- ➢ Reaction: Increased risk of bleeding.
- ➢ Clinical Significance: May cause serious bleeding complications.

- ❖ Ticagrelor + Metformin
- ➢ Reaction: Increased risk of lactic acidosis.
- ➢ Clinical Significance: Can worsen metabolic acidosis, especially in renal impairment.

- ❖ Torsemide + Spironolactone
- ➢ Reaction: Risk of hyperkalaemia or dehydration.
- ➢ Clinical Significance: Can cause serious electrolyte imbalances.

2. Moderate Interactions (Use with Caution)

- ❖ Metformin + Teneligliptin
- ➢ Reaction: Enhanced risk of hypoglycaemia.
- ➢ Clinical Significance: Needs monitoring for low blood sugar symptoms.

- ❖ Nikorandil + Aspirin
- ➢ Reaction: Increased risk of gastrointestinal ulcers or bleeding.
- ➢ Clinical Significance: Avoid in patients with a history of peptic ulcers.

- ❖ Atorvastatin + Ticagrelor
- ➢ Reaction: Increased statin toxicity.
- ➢ Clinical Significance: Can cause muscle pain, rhabdomyolysis**.**

FACTORS AFFECTING DRUG INTERACTIONS :

1. Patient-Related Factors

Drug clearance in a certain patient, age, genetics, gender, coexisting conditions, environmental circumstances, and food are all considered patient-related factors. Drug interactions become more important in patients who are too young or too old, have compromised immune systems, are taking medications that affect the cardiovascular or central nervous systems, have chronic illnesses, have multiple illnesses, or have renal or hepatic impairment. individuals with AIDS-related diseases, individuals with severe illnesses, and post-transplant patients are also more likely to experience drug interactions. Drug-drug interactions are more likely to occur in older adults with changed drug disposition, numerous diseases, and multiple medication use. Additionally, it is undoubtedly more difficult to recall taking multiple medicines at various times. (Identification and management of drug interactions, 2013) (S., 2008)[19,20]

2. Drug-Specific Factors :

The number of medications prescribed, their particular kinetic and dynamic characteristics, and the dosage, timing, order, formulation, and mode of administration are examples of drug-specific parameters. The likelihood of a drug interaction increases with the number of prescribers, the prevalence of alternative medicine use, and the use of medications that are more likely to cause drug interactions. The more prescriptions a patient takes, the higher the likelihood of drug interactions. Serious medication interactions are more likely to occur with drugs that have a low therapeutic index, or a narrow therapeutic range, meaning that the difference between the therapeutic and toxic doses is minimal. Warfarin, fluoroquinolones, antiepileptics, oral contraceptives, cisapride, and 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (HMG CoA-reductase inhibitors) were among the prevalent medicines that were involved in drug interactions. (JR., 2012) (Ament PW, 2000)[16,18]

Materials and Methodology:

Study Design -

This study follows an interpretation-based retrospective observational design to analyse drug-drug interactions (DDIs) in outpatient prescription records. The primary objective is to assess the frequency, severity, and clinical implications of DDIs.

Study Duration and Sample Size -

The study was conducted over three months, from 01/02/2025 to 1/03/2025, with a total of 70 outpatient prescriptions reviewed.

Data Collection -

Prescription data were extracted from electronic health records (EHRs) or manual prescription logs.

Pharmacy dispensing records provided the study's data. The pharmacy's database was used to get each patient's medical history, along with information about their medication dispensing (dosage, name, and dates of dispensing). In order to preserve patient privacy, this data was anonymised.

Drug Interaction Assessment: [Micromedex Software]

Inclusion Criteria:

- Prescription records with complete details, including drug names, dosage, and prescribing physician.
- Cases where drug interaction alerts were triggered in the EHR system.

Exclusion Criteria:

- Patients with incomplete prescription records.
- Prescriptions for single-drug therapy.

Interactions were categorized as:

1.**Major**: Life-threatening or requiring immediate intervention.

2.**Moderate**: May require dosage adjustment or monitoring.

3.**Minor**: Unlikely to cause significant clinical effects but noted for reference.

In this study, a random sample of 300 patients who had received at least four - five drug dispensing was constituted for each quarter between 01/02/2025 and 01/03/2015. The randomization was carried out used random numbers generator. For each patient, all drug 7g dispensed during the quarter of interest were considered.

Table No. 1: Drug-Drug Interaction

	Chemical Name	Frequency	Drug-Drug Interaction	Severity	Summary
1.	Metformin HCL	1-0-0	Aspirin-Ticagrelor	Major	Result in an increased risk of bleeding
	Teneligliptin	1-0-0	Aspirin-Torsemide	Major	Result in reduced diuretic effectiveness.
	Atorvastatin and Aspirin	1-0-0	Aspirin-Metformin HCl	Major	Result in increased risk of hypoglycaemia.
	Ticagrelor	1-0-0	Ranolazine-Metformin HCl	Major	Result in increased metformin exposure
	Nicorandil	1-0-0	Atorvastatin Calcium-Ranolazine	Moderate	Result in increased atorvastatin exposure
	Torsemide	1/2-0-0	Torsemide-Metformin HCl	Moderate	Result in an increased risk of hyperglycaemia
	Ranolazine	1-0-0			
2.	Glimepiride	1-0-0	Amiodarone HCl-Digoxin	Major	Result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
	Digoxin	1-0-0	Amiodarone HCl-Verapamil HCl	Major	Result in increased exposure of amiodarone
	Verapamil HCl	1-0-0	Digoxin-Omeprazole	Major	Result in digoxin exposure, an increased risk of digoxin toxicity
	Amiodarone HCl	1-0-0	Digoxin-Verapamil HCl	Major	Result in increased risk of complete heart block.
	Sacubitril	2-0-2	Amiodarone HCl-Glimepiride	Moderate	Result in increased plasma levels of glimepiride.
	Omeprazole Mg++	1-0-1			
3.	Digoxin	1-0-1	Amiodarone HCl - Digoxin	Major	Result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
	Spironolactone	1-0-0	Digoxin - Spironolactone	Major	Result in increased digoxin exposure.
	Tolvaptan	1-0-1	Digoxin - Tolvaptan	Major	Result in increased digoxin exposure.
	Doxofylline	1-0-0	Amiodarone HCl - Clonazepam	Moderate	Result in clonazepam toxicity (confusion, slurred speech)
	Amiodarone	1-0-1	Amiodarone HCl - Glimepiride	Moderate	Result in increased plasma levels of glimepiride.
	Glimepiride	1-0-1			
	Clonazepam	1-0-0			
4.	Atorvastatin	1-0-0	Linagliptin - Nebivolol HCl	Moderate	Result in hypoglycaemia or hyperglycaemia
	Metformin HCL	1-0-1	Nebivolol HCl - Metformin HCl	Moderate	Result in decreased symptoms of hypoglycaemia
	Linagliptin 5	1-0-0	Torsemide - Metformin HCl	Moderate	Result in an increased risk of hyperglycaemia
	Torsemide & Spironolactone	1-0-1			
	Nebivolol HCL	1-0-1			
	Rabeprazole & Domperidone	1-0-1			

5.	Carvedilol Calcium, Calcitriol & Vitamin K2 Ivermectin Clonidine	1-0-0 1-0-1 1-0-1 1-0-0	Carvedilol - Clonidine	Major	Result in an increased risk of worsen sinus node dysfunction and atrioventricular node conduction, an increased risk of bradycardia and AV block and an increased risk of hypotension.
6.	Gabapentin Domperidone & Naproxen Thiocolchicoside Omeprazole Sucralfate	1-0-0 1-0-1 1-0-0 1-0-1 1-0-1	Naproxen Sodium - Sucralfate	Moderate	Result in delayed absorption of naproxen.
7.	Omeprazole & Domperidone Hydroxyzine HCL Azithromycin Albendazole Cetirizine HCL	1-0-1 1-0-1 1-0-1 1-0-0 1-0-0	Azithromycin - Domperidone Azithromycin - Hydroxyzine HCl Domperidone - Hydroxyzine HCl	Major Major Major	Result in increased risk of QT interval prolongation. Result in an increased risk of QT interval prolongation. Result in an increased risk of QT interval prolongation.
8.	Doxycycline Hyclate & Lactic acid Azathioprine Dapsone Ferric phosphate	1-0-0 1-0-1 1-0-1 1-0-0	Doxycycline Hyclate - Ferric Phosphate	Moderate	Result in decreased tetracycline and iron effectiveness.
9.	Atorvastatin & Aspirin Metoprolol succinate Esomeprazole Vitamin B complex with B12 Moxifloxacin	1-0-1 1-0-0 1-0-0 1-0-1 1-0-0	Atorvastatin Calcium - Pyridoxine Aspirin - Metoprolol Succinate Aspirin - Thiamine	Major Moderate Moderate	Result in increased risk of myopathy and rhabdomyolysis. Result in reduced antihypertensive effect. Result in decreased salicylate effectiveness.

10.	Atorvastatin & Aspirin Voglibose, Glimepiride, Metformin HCL Dapaglifloxin	1-0-1 1-0-1 1-0-0 1-0-0	Aspirin - Glimepiride Aspirin - Metformin HCl Glimepiride - Metformin HCl	Major Major Major	Result in increased risk of hypoglycaemia. Result in increased risk of hypoglycaemia. Result in an increased risk of hypoglycaemia.
11.	Ursodiol Telmisartan Digoxin	1-0-1 1-0-0 1-0-0	Digoxin - Telmisartan	Major	Increased risk of digoxin toxicity
12.	Remogliflozin Etabonate Telmisartan Aspirin & Atorvastatin Metformin HCl & Glimepiride Vildagliptin Voglibose	1-0-1 1-0-0 1-0-0 1-0-0 1-0-0 1-0-0	Aspirin - Glimepiride Aspirin - Metformin HCl Glimepiride - Metformin HCl	Major Major Major	Result in increased risk of hypoglycaemia. Result in increased risk of hypoglycaemia. Result in an increased risk of hypoglycaemia.
13.	Metoprolol succinate Metformin HCL & Glimepiride Dapagliflozin & Sitagliptin Zinc & B complex & Vitamin C Digoxin Torsemide & Spironolactone	1-0-0 1-0-1 1-0-1 1-0-0 1-0-1 1-0-0	Amlodipine Besylate - Digoxin Dapagliflozin - Glimepiride Dapagliflozin - Metformin HCl Digoxin - Spironolactone Glimepiride - Metformin HCl	Major Major Major Major Major	Result in increased risk of complete heart block. Result in increased risk of hypoglycaemia. Result in increased risk of hypoglycaemia. Result in increased digoxin exposure. Result in an increased risk of hypoglycaemia.
14.	Metoprolol succinate Atorvastatin, Clopidogrel & Aspirin Torsemide & Spironolactone Escitalopram Pantoprazole & Domperidone Betahistine	1-0-0 1-0-1 1-0-0 1-0-0 1-0-1 1-0-0	Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Escitalopram Oxalate Aspirin - Spironolactone Aspirin - Torsemide Clopidogrel - Escitalopram Oxalate Domperidone - Escitalopram Oxalate Escitalopram Oxalate - Metoprolol Succinate	Major Major Major Major Major Major Major	Result in an increased risk of bleeding. Result in an increased risk of bleeding reduced diuretic effect Reduced diuretic effectiveness and possible nephrotoxicity. Result in an increased risk of bleeding. Result in an increased risk of QT interval prolongation. Result in increased CYP2D6 substrate exposure.

15.	Amiodaron Dapagliflozin & Sitagliptin Metoprolol Succinate Telmisartan Atorvastatin & Aspirin Torsemide Flupentixol & Melitracen	1-0-0 1-0-0 1-0-0 1-0-0 1-0-0 1-0-0 1-0-1	 ASPIRIN - TORSEMIDE AMIODARON HCL - ATORVASTATIN CALCIUM ASPIRIN - METOPROLOL SUCCINATE AMIODARON HCL - TORSEMIDE	Major Moderate Moderate Moderate	Reduced diuretic effectiveness and possible nephrotoxicity. Result in an increased risk of myopathy or rhabdomyolysis. Result in reduced antihypertensive effect. Result in increased plasma levels of torsemide.
16.	Metoprolol Succinate Tenegliptin & Dapagliflozin Telmisartan & Chlorthalidone Atorvastatin & Aspirin	1-0-1 1-0-0 1-0-0 1-0-1	Aspirin - Chlorthalidone Chlorthalidone - Dapagliflozin Aspirin - Metoprolol Succinate Dapagliflozin - Metoprolol Succinate	Major Major Moderate Moderate	Reduced diuretic effectiveness and possible nephrotoxicity. Increased risk of hyperglycaemia and an increased insulin. Result in reduced antihypertensive effect. hyperglycaemia; decreased symptoms of hypoglycaemia.
17.	Atorvastatin & Aspirin Carvedilol phosphate Silodosin Torsemide Zinc & B complex with Vitamin C	1-0-1 1-0-0 1-0-0 1-0-0 1-0-1	 ASPIRIN - TORSEMIDE ASPIRIN - CARVEDILOL PHOSPHATE	Major Moderate	Reduced diuretic effectiveness and possible nephrotoxicity. Result in reduced antihypertensive effect.
18.	Metformin HCL & Glimepiride Atorvastatin & Aspirin Metoprolol succinate Carbamazepine Escitalopram Oxalate & Clonazepam	1-0-0 1-0-1 1-0-0 1-0-0 1-0-1	Aspirin - Escitalopram Oxalate Aspirin - Glimepiride Aspirin - Metformin HCl Atorvastatin Calcium - Carbamazepine Carbamazepine - Clonazepam Carbamazepine - Escitalopram Oxalate Carbamazepine - Glimepiride Escitalopram Oxalate - Metoprolol Succinate Glimepiride - Metformin HCl	Major Major Major Major Major Major Major Major Major	Result in an increased risk of bleeding. Result in increased risk of hypoglycaemia. Result in increased risk of hypoglycaemia. Reduced CYP3A4 substrate exposure. Result in reduced clonazepam exposure. Result in reduced escitalopram exposure. Result in reduced CYP2C9 substrate exposure. Result in increased CYP2D6 substrate exposure. Result in an increased risk of hypoglycaemia.
19.	Metoprolol Succinate ER Telmisartan and Cilnidipine Calcium and Cholecalciferol Naproxen Pantoprazole and domperidone	1-0-0 1-0-0 1-0-1 1-0-1 1-0-0	Domperidone - Escitalopram Oxalate Escitalopram Oxalate - Metoprolol Succinate Escitalopram Oxalate - Naproxen Metoprolol Succinate - Naproxen Naproxen - Telmisartan	Major Major Major Moderate Moderate	Result in an increased risk of QT interval prolongation Result in increased CYP2D6 substrate exposure Result in an increased risk in bleeding Result in reduced antihypertensive effect

	Escitalopram oxalate and Clonazepam	 0-0-1			Result in reduced antihypertensive effect and renal dysfunction and increased blood pressure
20.	Hydroxychloroquine Deflazacort Methotrexate Naproxen Levocetirizine HCL Montelukast and Ambroxol HCL Doxofylline Ferrous Fumarate and Folic acid	1-0-0 1-0-1 1-0-0 1-0-0 1-0-1 1-0-1 1-0-0	Deflazacort - Naproxen Folic Acid- Methotrexate Hydroxychloroquine Sulphate - Methotrexate Methotrexate - Naproxen	Major Major Major Major	Result in increased risk of gastrointestinal ulcer or bleeding Result in reduced folic acid serum level Increased risk of methotrexate related adverse reactions Result in methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)
21.	Cilnidipine and Metoprolol Succinate Aspirin gastro resistant and Atorvastatin Pantoprazole sodium Succinate Levosulpride Calcium and Vit D3	1-0-0 1-0-0 1-0-0 1-0-1	Calcium - Aspirin Calcium/Cholecalciferol - Aspirin	Moderate Moderate	Result in decreased salicylate effectiveness Result in decreased Salicylate effectiveness
22.	Carbamazepine Telmisartan Metoprolol Extended released Atorvastatin and Aspirin Metformin HCL SR and Glimepiride	1-0-1 1-0-0 0-0-1 0-0-1 1-0-0	Aspirin - Glimepiride Aspirin -Metformin HCl Carbamazepine - Glimepiride Glimepiride - Metformin HCl Aspirin -Metoprolol Succinate Glimepiride - Metoprolol Succinate Metoprolol Succinate - Metformin HCl	Major Major Major Major Moderate Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in reduced CYP2C9 substrate exposure Result in increased risk of hypoglycaemia Result in reduced antihypertensive effect Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia
23.	Mesalazine prolonged release Mebeverine HCL and Chlordiazepoxide Metoprolol Succinate ER Omeprazole and Domperidone Naproxen	0-0-1 1-0-0 1-0-0 1-0-0 1-0-1 1-0-1	Metoprolol Succinate - Naproxen	Moderate	Result in reduced antihypertensive effect

24.	Teneligliptin and Dapagliflozin Telmisartan and Chlorthalidone Metoprolol Succinate ER and Amlodipine Atorvastatin and Aspirin Glimepiride and Metformin HCL and Voglibose	1-0-0 1-0-1 1-0-0 1-0-0 1-0-1	Aspirin - Chlorthalidone Aspirin - Glimepiride Aspirin - Metformin HCl Chlorthalidone - Dapagliflozin Chlorthalidone - Glimepiride Glimepiride - Metformin HCl Amlodipine - Metformin HCl Aspirin - Metoprolol Succinate Chlorthalidone - Metformin HCl Dapagliflozin Propanediol - Metoprolol Succinate Glimepiride - Metoprolol Succinate Metoprolol Succinate - Metformin HCl	Major Major Major Major Major Major Moderate Moderate Moderate Moderate Moderate Moderate	Result in reduced diuretic effectiveness Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in an increased risk of hyperglycaemia Result in increased risk of hyperglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in reduced antihypertensive effect Result in increased risk of hyperglycaemia Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia decreased symptoms of hypoglycaemia
25.	Metoprolol Succinate ER and Amlodipine Atorvastatin and Aspirin Glimepiride and pioglitazone	1-0-0 1-0-0 0-0-1	Aspirin - Glimepiride Aspirin - Metformin HCl Glimepiride - Metformin HCl Glimepiride - Pioglitazone HCl Metformin HCl - Pioglitazone HCl Amlodipine - Metformin HCl Atorvastatin Calcium - Pioglitazone HCl	Major Major Major Major Major Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in decreased pioglitazone serum concentrations
26.	Metoprolol Succinate ER Atorvastatin and Aspirin and Clopidogrel Torsemide and Spironolactone Escitalopram Betahistine dihydrochloride Pantoprazole and Domperidone	0-0-1 0-0-1 1-0-1 0-0-1 1-0-0 1-0-0	Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Escitalopram Oxalate Aspirin - Spironolactone Aspirin - Torsemide Clopidogrel Hydrogen Sulphate -Escitalopram Oxalate Domperidone - Escitalopram Oxalate Atorvastatin Calcium - Clopidogrel Hydrogen Sulphate Clopidogrel Hydrogen Sulphate - Torsemide	Major Major Major Major Major Major Moderate Moderate	Result in increased risk of bleeding Result in increased risk of bleeding Result in reduced diuretic effectiveness, hyperkalaemia . Result in reduced diuretic effectiveness Result in increased risk of bleeding Result in increased risk of QT interval prolongation Result in decreased formation of Clopidogrel active metabolite Result in increased risk of torsemide toxicity (nausea, dizziness, headache, fatigue, skin rash, muscle cramps and increases in serum uric acid and creatinine)

27.	Teneligliptin and Dapagliflozin Cilnidipine Metformin HCL and Glimepiride Rosuvastatin Aspirin and Clopidogrel Pantoprazole and Domperidone	1-0-0 1-0-0 0-0-1 1-0-0 1-0-0	Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Glimepiride Aspirin - Metformin HCl Glimepiride -Metformin HCl	Major Major Major Major	Result in increased risk of bleeding Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
28.	Glimepiride Teneligliptin and Dapagliflozin Sodium Bicarbonate Metformin HCL SR Metoprolol Succinate ER and Amlodipine	1-0-0 1-0-0 1-0-1 1-0-0 1-0-0	Dapagliflozin - Glimepiride Dapagliflozin - Metformin HCl Glimepiride -Metformin HCl Amlodipine - Metformin HCl Dapagliflozin - Metoprolol Succinate Glimepiride - Metoprolol Succinate Metformin HCl - Metoprolol Succinate	Major Major Major Moderate Moderate Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia
29.	Atorvastatin and Clopidogrel Isosorbide-5- Mononitrate Torsemide and Spironolactone Doxofylline	1-0-0 1-0-0 1-0-0 1-0-1	Atorvastatin Calcium - Clopidogrel Hydrogen Sulphate Clopidogrel Hydrogen Sulphate - Torsemide	Moderate Moderate	Result in decreased formation of Clopidogrel active metabolite Result in increased risk of torsemide toxicity (nausea, dizziness)
30.	Atorvastatin and Aspirin Silodosin Torsemide Carvedilol Phosphate	1-0-0 1-0-1 1-0-0 1-0-0	Aspirin - Torsemide Aspirin - Carvedilol Phosphate	Major Moderate	Result in reduced diuretic effectiveness Result in reduced antihypertensive effect
31.	Metoprolol Succinate ER and Amlodipine Telmisartan and Chlorthalidone Prazosin HCL OPS Atorvastatin and Clopidogrel and Aspirin Voglibose Glimepiride and Metformin HCL Dapagliflozin and Sitagliptin Phosphate Betahistine	1-0-0 1-0-1 1-0-0 0-0-1 1-0-0 1-0-0	Amlodipine - Clopidogrel Hydrogen Sulphate Amlodipine - Domperidone Aspirin - Chlorthalidone Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Glimepiride Aspirin - Metformin HCl Chlorthalidone - Dapagliflozin Chlorthalidone - Glimepiride Chlorthalidone - Sitagliptin Phosphate Dapagliflozin - Glimepiride Dapagliflozin - Metformin HCl	Major Major Major Major Major Major Major Major Major Major Major	Result in decreased antiplatelet effect Result in increased Domperidone exposure Result in reduced diuretic effectiveness Result in increased risk of bleeding Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in an increased risk of hyperglycaemia Result in an increased risk of hyperglycaemia Result in an increased risk of hyperglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia

	Pantoprazole and Domperidone	1-0-0	Glimepiride - Metformin HCl	Major	Result in increased risk of hypoglycaemia
			Glimepiride - Sitagliptin Phosphate	Major	Result in increased risk of hypoglycaemia
			Metformin HCl -Sitagliptin Phosphate	Major	Result in increased risk of hypoglycaemia
			Amlodipine - Metformin HCl	Moderate	Result in increased risk of hyperglycaemia
			Aspirin - Metoprolol Succinate	Moderate	Result in reduced antihypertensive effect
			Atorvastatin Calcium - Clopidogrel Hydrogen Sulphate	Moderate	Result in decreased formation of Clopidogrel active metabolite
			Chlorthalidone - Metformin HCl	Moderate	Result in increased risk of hyperglycaemia
			Dapagliflozin - Metoprolol Succinate	Moderate	Result in hypoglycaemia or hyperglycaemia
			Glimepiride - Metoprolol Succinate	Moderate	Result in hypoglycaemia or hyperglycaemia
			Metformin HCl - Metoprolol Succinate	Moderate	Result in decreased symptoms of hypoglycaemia
			Metoprolol Succinate - Prazosin HCl	Moderate	Result in an exaggerated hypotensive response to the first dose of the alpha blocker
			Metoprolol Succinate - Sitagliptin Phosphate		
32.	Leflunomide	0-0-1	Deflazacort - Naproxen Sodium	Major	Result in increased risk of gastrointestinal ulcer or bleeding
	Deflazacort	1-0-1			
	Naproxen	1-0-1			
	Omeprazole and Domperidone	1-0-0			
33.	Aspirin and Atorvastatin	1-0-0	Aspirin - Chlorthalidone	Major	Result in reduced diuretic effectiveness and nephrotoxicity
	Propranolol	1-0-0	Aspirin - Rivaroxaban	Major	Result in increased risk of bleeding
	Telmisartan and Chlorthalidone	0-0-1	Aspirin - Propranolol HCl	Moderate	Result in reduced antihypertensive effect
	Rivaroxaban	1-0-0	Aspirin - Ranitidine HCl	Minor	Result in reduced salicylate plasma levels and decreased antiplatelet effect of Aspirin
	Ranitidine	1-0-0			
34.	Dapagliflozin and Sitagliptin and Metformin HCL	1-0-0	Aspirin - Clopidogrel Hydrogen Sulphate	Major	Result in an increased risk of bleeding
			Aspirin - Metformin HCl	Major	Result in increased risk of hypoglycaemia
	Rosuvastatin Aspirin and Clopidogrel	1-0-0	Dapagliflozin - Metformin HCl	Major	Result in increased risk of hypoglycaemia
	Telmisartan and Cilnidipine and Metoprolol Succinate	1-0-0	Aspirin - Metoprolol Succinate	Moderate	Result in reduced antihypertensive effect
			Dapagliflozin - Metoprolol Succinate	Moderate	Result in hypoglycaemia or hyperglycaemia
	Metformin HCL	1-0-1	Metoprolol Succinate - Metformin HCl	Moderate	Result in decreased symptoms of hypoglycaemia

35.	Cilnidipine and Metoprolol Succinate Atorvastatin and Aspirin Pantoprazole and Levosulpride	1-0-0 1-0-0 1-0-0	Aspirin - Metoprolol Succinate	Moderate	Result in reduced antihypertensive effect
36.	Metoprolol Succinate and Amlodipine Atorvastatin and Aspirin and Clopidogrel Metformin HCL and Glimepiride	1-0-0 1-0-0 1-0-0	Amlodipine - Clopidogrel Hydrogen Sulphate Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Glimepiride Aspirin - Metformin HCl Glimepiride -Metformin HCl Amlodipine - Metformin HCl Aspirin - Metoprolol Succinate Atorvastatin Calcium- Clopidogrel Hydrogen Sulphate Glimepiride - Metoprolol Succinate Metoprolol Succinate - Metformin HCl	Major Major Major Major Major Moderate Moderate Moderate Moderate Moderate	Result in decreased antiplatelet effect Result in an increased risk of bleeding Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in reduced antihypertensive effect Result in decreased formation of Clopidogrel active metabolite Result in hypoglycaemia or hyperglycaemia Result in decreased symptoms of hypoglycaemia
37.	Metformin HCL and Glimepiride Rosuvastatin Clopidogrel and Aspirin Gabapentin and Nortriptyline Teneligliptin and Dapagliflozin Rabeprazole and Domperidone	1-0-0 1-0-0 0-0-1 1-0-0 1-0-0	Aspirin - Glimepiride Aspirin - Nortriptyline HCl Aspirin - Metformin HCl Dapagliflozin - Glimepiride Dapagliflozin - Metformin HCl Domperidone - Nortriptyline HCl Glimepiride - Metformin HCl	Major Major Major Major Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of bleeding Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of QT interval prolongation Result in increased risk of hypoglycaemia
38.	Dapagliflozin and Sitagliptin Metformin HCL Rosuvastatin and Fenofibrate Metformin HCL and Glimepiride	1-0-0 1-0-0 1-0-1	Dapagliflozin - Glimepiride Dapagliflozin - Metformin HCl Fenofibrate - Rosuvastatin Calcium Glimepiride - Sitagliptin Glimepiride - Metformin HCl Sitagliptin - Metformin HCl Fenofibrate - Glimepiride	Major Major Major Major Major Major Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of myopathy or rhabdomyolysis Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased Glimepiride exposure and increased blood glucose lowering effect and risk of hypoglycaemia

39.	Hydroxychloroquine Deflazacort Methotrexate Tofacitinib Naproxen Levocetirizine HCL Montelukast and Ambroxol Doxofylline Pirfenidone Ferrous Fumarate and Folic acid	1-0-1 1-0-1 1-0-0 1-0-0 1-0-1 1-0-1 1-0-1 1-0-0 1-0-0	Deflazacort - Naproxen Folic Acid - Methotrexate Hydroxychloroquine Sulphate – Methotrexate Methotrexate - Naproxen	Major Major Major Major	Result in increased risk of gastrointestinal ulcer or bleeding Result in reduced folic acid serum level Result in increased methotrexate exposure, and increased risk of methotrexate related severe adverse reactions, reduced active metabolite formation and possibly reduced methotrexate efficacy Result in methotrexate toxicity (leukopenia, thrombocytopenia, anaemia, nephrotoxicity, mucosal ulcerations)
40.	Glimepiride Voglibose and Metformin Vildagliptin Amlodipine and Atenolol Omeprazole and Domperidone	1-0-1 1-0-0 0-0-1 1-0-0	Amlodipine - Domperidone Glimepiride - Metformin HCl Amlodipine - Metformin HCl Atenolol - Glimepiride Atenolol - Vildagliptin Atenolol - Metformin HCl	Major Major Moderate Moderate Moderate Moderate	Result in increased Domperidone exposure Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in hypoglycaemia or hyperglycaemia Result in decreased symptoms of hypoglycaemia Result in decreased symptoms of hypoglycaemia
41.	Metoprolol Succinate and Amlodipine Atorvastatin and Aspirin Escitalopram Oxalate and Clonazepam Multivitamin and multimineral and antioxidant Rabeprazole and Domperidone	1-0-0 1-0-0 0-0-1 1-0-0 1-0-0	Amlodipine - Domperidone Aspirin - Escitalopram Oxalate Domperidone - Escitalopram Oxalate Escitalopram Oxalate - Metoprolol Succinate Aspirin - Metoprolol Succinate	Major Major Major Major Moderate	Result in increased Domperidone exposure Result in increased risk of bleeding Result in increased risk of QT interval prolongation Result in increased CYP2D6 substrate exposure Result in antihypertensive effect
42.	Gliclazide and Metformin HCL Metoprolol Succinate ER Teneligliptin and Dapagliflozin Atorvastatin and Aspirin	1-0-0 1-0-0 1-0-1 1-0-0	Aspirin - Metformin HCl Dapagliflozin - Metformin HCl Aspirin - Metoprolol Succinate Dapagliflozin - Metoprolol Succinate Metoprolol Succinate - Metformin HCl	Major Major Moderate Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in reduced antihypertensive effect Result in hypoglycaemia or hyperglycaemia Result in decreased symptoms of hypoglycaemia

43.	Metoprolol succinate ER and Chlorthalidone Betahistine Atorvastatin and Aspirin Tamsulosin HCL Omeprazole and Domperidone	1-0-0 0-0-1 1-0-0 0-0-1 1-0-0	Aspirin - Chlorthalidone Aspirin - Metoprolol Succinate Metoprolol Succinate - Tamsulosin HCl	Major Moderate Moderate	Result in reduced diuretics effectiveness Result in reduced antihypertensive effect Result in exaggerated hypertensive response to the first dose of the alpha blocker
44.	Doxofylline Atorvastatin and Aspirin Amiodarone Glimepiride Omeprazole	1-0-0 1-0-0 0-0-1 1-0-0 1-0-0	Aspirin - Glimepiride Amiodarone HCl - Atorvastatin Calcium Amiodarone HCl - Glimepiride	Major Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of myopathy or rhabdomyolysis Result in increased plasma level of Glimepiride
45.	Glimepiride Voglibose and Metformin ER Cilnidipine and Telmisartan Dapagliflozin and Sitagliptin phosphate Atorvastatin and Aspirin Pantoprazole and Domperidone	1-0-1 1-0-0 1-0-0 1-0-0 1-0-0	Aspirin - Glimepiride Aspirin - Metformin Hydrochloride Glimepiride - Sitagliptin Phosphate Glimepiride - Metformin Hcl Sitagliptin Phosphate - Metformin Hydrochloride	Major Major Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
46.	Metoprolol succinate ER Atorvastatin and Aspirin Rabeprazole Sodium and Domperidone	0-0-1 0-0-1 0-0-1	Aspirin - Metoprolol Succinate	Moderate	Result in reduced antihypertensive effect
47.	Clopidogrel and Aspirin Atorvastatin Telmisartan and Chlorthalidone	1-0-0 1-0-0 0-0-1	Aspirin - Chlorthalidone Aspirin - Clopidogrel Hydrogen Sulphate Atorvastatin Calcium - Clopidogrel Hydrogen Sulphate	Major Major Moderate	Reduced diuretics effectiveness and possible nephrotoxicity Result in increased risk of bleeding Decreased formation of clopidogrel active metabolite
48.	Ticagrelor Teneligliptin and Dapagliflozin Metformin HCl and Glimepiride	1-0-1 1-0-0 0-0-1	Dapagliflozin - Glimepiride Dapagliflozin - Metformin Hydrochloride Glimepiride - Metformin Hydrochloride	Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
49.	Febuxostat Naproxen Deflazacort	1-0-0 1-0-1 1-0-1	Deflazacort - Naproxen Sodium Escitalopram Oxalate - Methotrexate Escitalopram Oxalate - Naproxen Sodium	Major Major Major	Result in increased risk of gastrointestinal ulcer or bleeding Result in increased methotrexate exposure Result in increased risk of bleeding

	Escitalopram Oxalate and Clonazepam Methotrexate	0-0-1 Once a week	Febuxostat - Methotrexate Methotrexate - Naproxen Sodium	Major Major	Increased risk of methotrexate related adverse reactions Result in methotrexate toxicity (leukopenia, thrombocytopenia)
50.	Metformin HCL Dapagliflozin and Sitagliptin phosphate Rosuvastatin and Clopidogrel Metformin HCL and Glimepiride Voglibose	1-0-0 0-0-1 0-0-1 0-0-1	Dapagliflozin - Glimepiride Dapagliflozin - Metformin Hydrochloride Glimepiride - Sitagliptin Glimepiride - Metformin Hydrochloride Sitagliptin - Metformin Hydrochloride	Major Major Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
51.	Pregabalin and Nortriptyline Vitamin B Complex Metformin HCL and Glimepiride	0-0-1 1-0-1 0-0-1	Glimepiride - Metformin Hydrochloride	Major	Result in increased risk of hypoglycaemia
52.	Metoprolol succinate and Amlodipine Telmisartan and Chlorthalidone Metformin HCL and Glimepiride Linagliptin and Dapagliflozin Atorvastatin Clopidogrel and Aspirin	0-0-1 1-0-0 1-0-0 1-0-0 1-0-0	Amlodipine - Clopidogrel Hydrogen Sulphate Aspirin - Chlorthalidone Aspirin - Clopidogrel Hydrogen Sulphate Aspirin - Glimepiride Aspirin - Metformin Hydrochloride Chlorthalidone - Dapagliflozin Chlorthalidone - Glimepiride Chlorthalidone - Linagliptin Dapagliflozin - Glimepiride Dapagliflozin - Metformin Hydrochloride Glimepiride - Metformin Hydrochloride	Major Major Major Major Major Major Major Major Major Major Major	Result in decreased antiplatelet effect Result in reduced diuretics effectiveness Result in increased risk of bleeding Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hyperglycaemia Result in increased risk of hyperglycaemia Result in increased risk of hyperglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
53.	Metoprolol succinate Telmisartan and Chlorthalidone Escitalopram Oxalate and Clonazepam Doxofylline Montelukast sodium and Levocetirizine HCL	0-0-1 1-0-0 0-0-1 1-0-1 1-0-1	Clonazepam - Levocetirizine Dihydrochloride Escitalopram Oxalate - Metoprolol Succinate	Major Major	Result in increased risk of CNA depression Result in increased CYP2D6 substrate exposure
54.	Ticagrelor Atorvastatin and Aspirin Metformin HCL and Glimepiride	1-0-1 1-0-0 0-0-1	Aspirin - Glimepiride Aspirin - Ticagrelor Aspirin - Metformin Hydrochloride	Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of bleeding Result in increased risk of hypoglycaemia

	Telmisartan	0-0-1	Glimepiride - Metformin Hydrochloride	Major	Result in increased risk of hypoglycaemia
55.	Thyroxine Sodium Amlodipine and Atenolol Aspirin and Atorvastatin	1-0-0 0-0-1 0-0-1	Aspirin - Atenolol	Moderate	Result in reduced antihypertensive effect
56.	Aspirin Ticagrelor Atorvastatin Isosorbide Mononitrate Metoprolol ER	0-0-1 1-0-1 0-0-1 1-0-0 0-0-1	Aspirin - Ticagrelor Aspirin - Metoprolol Succinate	Major Moderate	Result in increased risk of bleeding Result in reduced antihypertensive effect
57.	Atorvastatin Clopidogrel and Aspirin Glimepiride Metformin HCL and Voglibose Dapagliflozin and Sitagliptin phosphate Omeprazole and Domperidone	0-0-1 1-0-0 1-0-0 1-0-0	Aspirin - Glimepiride Aspirin - Metformin Hydrochloride Dapagliflozin - Glimepiride Dapagliflozin - Metformin Hydrochloride Glimepiride - Sitagliptin Glimepiride - Metformin Hydrochloride Sitagliptin - Metformin Hydrochloride	Major Major Major Major Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia
58.	Telmisartan and Cilnidipine and Metoprolol succinate Telmisartan and Cilnidipine Metformin HCL and Glimepiride	0-0-1 1-0-0 0-0-1	Glimepiride - Metformin Hydrochloride Glimepiride - Metoprolol Succinate Metoprolol Succinate - Metformin Hydrochloride	Major Moderate Moderate	Result in increased risk of hypoglycaemia Result in hypoglycaemia or hyperglycaemia Result in hypoglycaemia or hyperglycaemia
59.	Metoprolol succinate and Amlodipine Aspirin and Atorvastatin Ticagrelor Amiodarone Ramipril	0-0-1 0-0-1 1-0-1 0-0-1 0-0-1	Amiodarone HCl - Ticagrelor Aspirin - Ticagrelor Amiodarone HCl - Atorvastatin Calcium Aspirin - Metoprolol Succinate	Major Major Moderate Moderate	Result in increased amiodarone and ticagrelor exposure Result in increased risk of bleeding Result in increased risk of myopathy or rhabdomyolysis Result in reduced antihypertensive effect
60.	Thyroxine Sodium Amlodipine and Atenolol Aspirin and Atorvastatin	0-0-1 0-0-1 0-0-1	Aspirin - Atenolol	Moderate	May result in reduced antihypertensive effect

61.	Metoprolol succinate and Amlodipine Atorvastatin and Aspirin Metformin HCL and Glimepiride Prazosin HCL	0-0-1 0-0-1 1-0-0 0-0-1	Aspirin - Glimepiride Aspirin - Metformin Hydrochloride Glimepiride - Metformin Hydrochloride Amlodipine - Metformin Hydrochloride Aspirin - Metoprolol Succinate Glimepiride - Metoprolol Succinate Metoprolol Succinate - Prazosin HCl Metoprolol Succinate - Metformin Hydrochloride	Major Major Major Moderate Moderate Moderate Moderate Moderate	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in reduced antihypertensive effect Result in hypoglycaemia or hyperglycaemia Exaggerated hypotensive response to first dose of alpha blocker Result in hypoglycaemia or hyperglycaemia
62.	Esomeprazole Axitinib Thiamine Nitrate Pyridoxine HCL Propranolol	0-0-1 1-0-0 0-0-1 0-0-1	Esomeprazole Sodium - Propranolol HCl	Moderate	Result in increased propranolol exposure
63.	Itraconazole Levocetirizine HCL Methyl Prednisolone Luliconazole	1-0-1 0-0-1 1-0-1 1-0-1	Itraconazole - Methyl Prednisolone	Major	Result in increased methyl Prednisolone exposure and an increased risk of methyl Prednisolone related adverse effects
65.	Metformin HCL and Glimepiride Metoprolol ER Atorvastatin and Aspirin Carbamazepine Omeprazole and Domperidone	1-0-0 0-0-1 0-0-1 1-0-1 1-0-0	Aspirin - Glimepiride Aspirin - Metformin Hydrochloride Atorvastatin Calcium - Carbamazepine Carbamazepine - Domperidone Carbamazepine - Glimepiride Carbamazepine - Omeprazole Glimepiride - Metformin Hydrochloride	Major Major Major Major Major Major Major	Result in increased risk of hypoglycaemia Result in increased risk of hypoglycaemia Result in reduced CYP3A4 substrate exposure Result in reduced CYP3A4 substrate exposure Result in reduced CYP2C9 substrate exposure Result in increased risk of carbamazepine toxicity Result in increased risk of hypoglycaemia
66.	Atorvastatin and Aspirin Carvedilol Phosphate ER Silodosin And Dutasteride Torsemide Omeprazole and Domperidone	0-0-1 1-0-0 0-0-1 0-0-1 1-0-0	Aspirin - Torsemide Aspirin - Carvedilol Phosphate	Major Moderate	Result in reduced diuretics effectiveness Result in reduced antihypertensive effect
67.	Ethambutol Rifampin and Isoniazid Omeprazole and Domperidone	1-0-0 1-0-0 1-0-0	Domperidone - Isoniazid Isoniazid - Rifampin Omeprazole - Rifampin	Major Major Major	Result in increased Domperidone exposure Result in increased risk of hepatotoxicity Result in reduced Omeprazole exposure

68.	Amoxycillin Potassium Aceclofenac Paracetamol Rabeprazole Sodium and Domperidone	1-0-0 1-0-0 1-0-1	Aceclofenac - Deflazacort	Major	Result in increased risk of gastrointestinal ulcer or bleeding
69.	Cefixime Levocetirizine HCL and Montelukast sodium Aceclofenac Paracetamol and Serratiopeptidase Deflazacort Omeprazole and Domperidone	1-0-1 1-0-1 1-0-1 1-0-1 1-0-0	Aceclofenac - Deflazacort	Major	Result in increased risk of gastrointestinal ulcer or bleeding
70.	Hydroxyzine HCL Levofloxacin Phenylephrine HCL and Chlorpheniramine Maleate Ranitidine and Domperidone	0-0-1 1-0-1 1-0-1 1-0-0	Domperidone - Hydroxyzine HCl Domperidone - Levofloxacin Domperidone - Ranitidine HCl Hydroxyzine HCl - Levofloxacin	Major Major Major Major	Result in increased risk of QT interval prolongation Result in increased risk of QT interval prolongation Result in increased risk of QT interval prolongation Result in increased risk of QT interval prolongation

Result & Discussion :

1) Distribution of DDI Severity

A total of 70 outpatient prescriptions were reviewed during the study period, spanning from February 1st, 2025, to March 1st, 2025. These prescriptions were analysed using the Micromedex drug interaction database to identify potential drug-drug interactions (DDIs)."

A total of 299 drug-drug interactions (DDIs) were identified from the outpatient prescriptions analysed during the study period. These interactions were categorized into three levels of clinical severity: major, moderate, and minor, based on standard criteria provided by the Micromedex database.

Major interactions: 207 (69.2%)

Moderate interactions: 91 (30.4%)

Minor interactions: 1 (0.3%)

The data is visually represented in Figure 1, which shows the predominance of major DDIs, indicating a potentially high clinical risk in the outpatient setting.

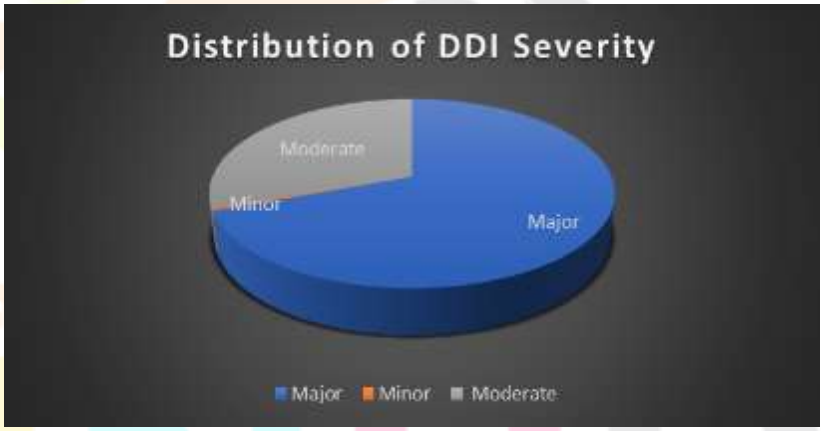


Fig. No. 01

Discussion :

This study found a high number of drug-drug interactions in outpatient prescriptions. Most (69.2%) were major and could lead to serious health problems if not managed properly. Moderate interactions (30.4%) also need attention, while one minor interaction was noted. These results match earlier studies showing that many DDIs go unnoticed in outpatient care.

2) Frequency of Drug Combination Involving Aspirin

Among the analysed prescriptions, aspirin was involved in several drug combinations. The most frequent combinations were:

Aspirin + Metformin HCL (18 times)

Aspirin + Glimepiride (16 times)

Aspirin + Metoprolol Succinate (14 times)

Aspirin + Clopidogrel (8 times)

Other combinations occurred less frequently (2–7 times each).

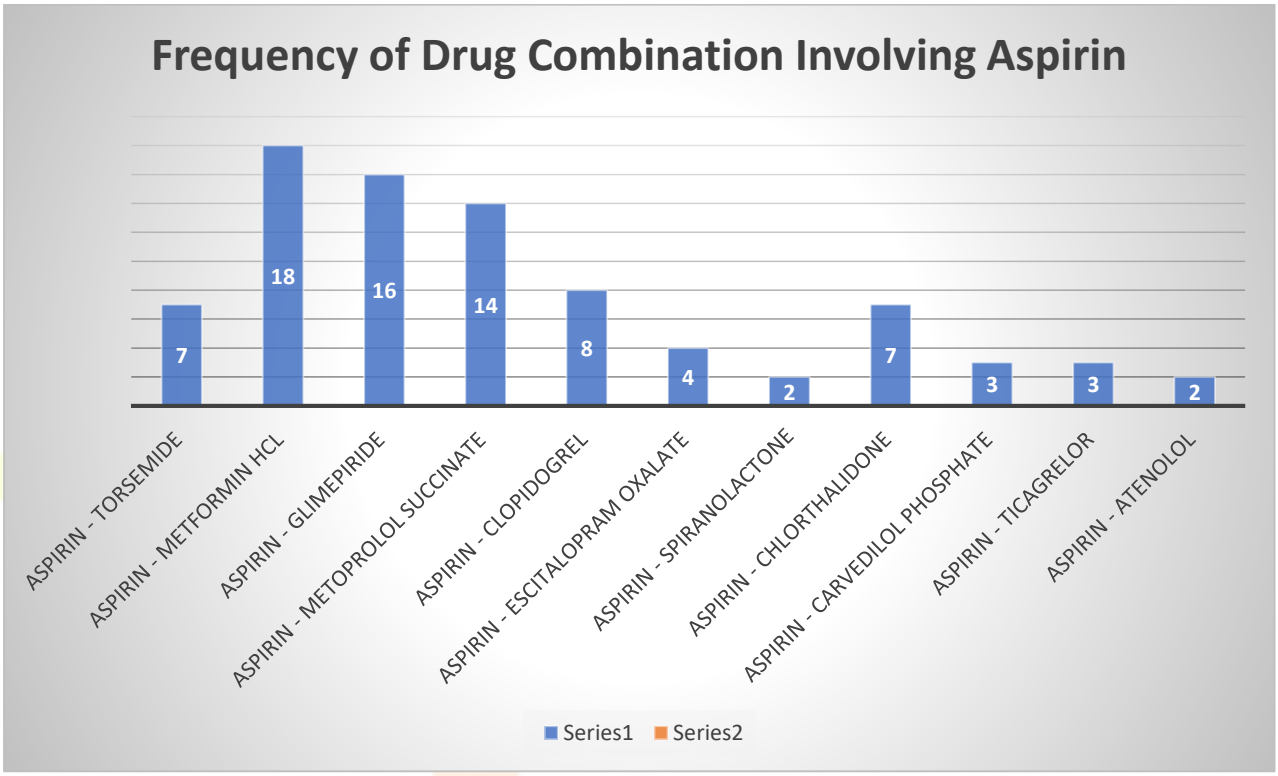


Fig. No. 02

Discussion :

Aspirin was mostly combined with diabetes and heart medicines. The most common was aspirin + metformin, which may cause stomach problems or bleeding, especially in older patients. Aspirin + clopidogrel is also risky due to bleeding. These findings show the need to carefully check such combinations to avoid harm.

3) No.of DDI Involving Glimepiride Combinations

The analysis of outpatient prescriptions revealed notable drug-drug interactions (DDIs) involving Glimepiride when co-prescribed with other commonly used medications. The graphical representation above illustrates the frequency of DDIs among three specific Glimepiride combinations:

Glimepiride + Metformin HCL: 24 DDIs

Glimepiride + Metoprolol Succinate: 7 DDIs

Glimepiride + Sitagliptin: 5 DDIs

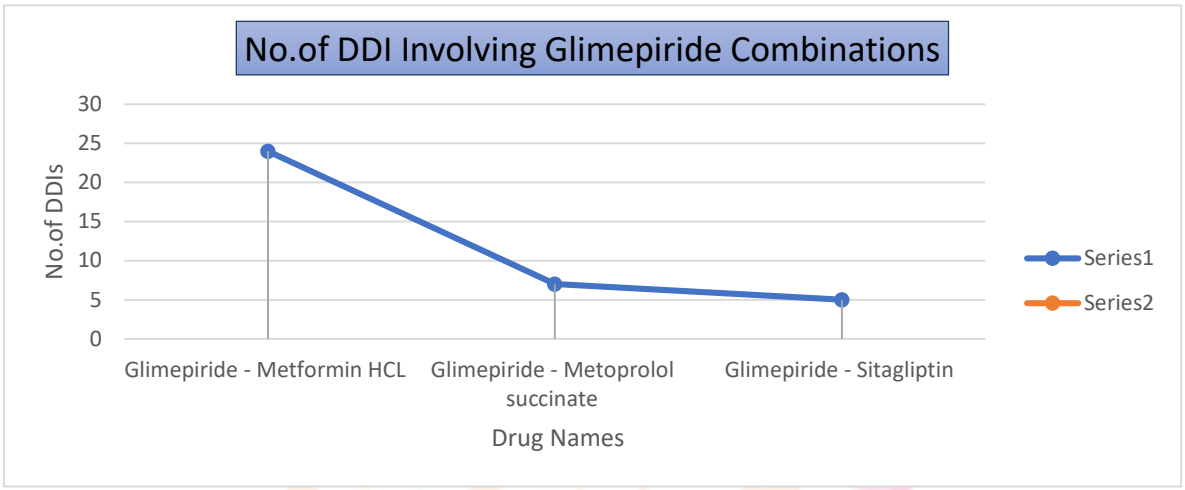


Fig. No. 03

Discussion :

The analysis shows that the Glimepiride–Metformin HCL combination had the highest number of DDIs (24), likely due to their common use in type 2 diabetes and the risk of enhanced hypoglycaemia. Glimepiride–Metoprolol Succinate (7 DDIs) also posed a risk, as beta-blockers can mask hypoglycaemia symptoms, delaying detection. The Glimepiride–Sitagliptin combination had the fewest interactions (5), suggesting a relatively safer profile, though hypoglycaemia is still possible.

These results emphasize the importance of monitoring and patient counselling in outpatient settings, especially when using Glimepiride with other antidiabetic or cardiovascular drugs.

4) DDI Involving Dapaglifloxin Combination

The graph titled "DDI Involving Dapagliflozin Combination" illustrates the frequency of drug-drug interactions (DDIs) involving dapagliflozin when prescribed in combination with three commonly co-administered drugs: Metformin HCL, Metoprolol, and Glimepiride.

Among the combinations:

Dapagliflozin + Metformin HCL exhibited the highest number of potential interactions, with a total of 11 instances.

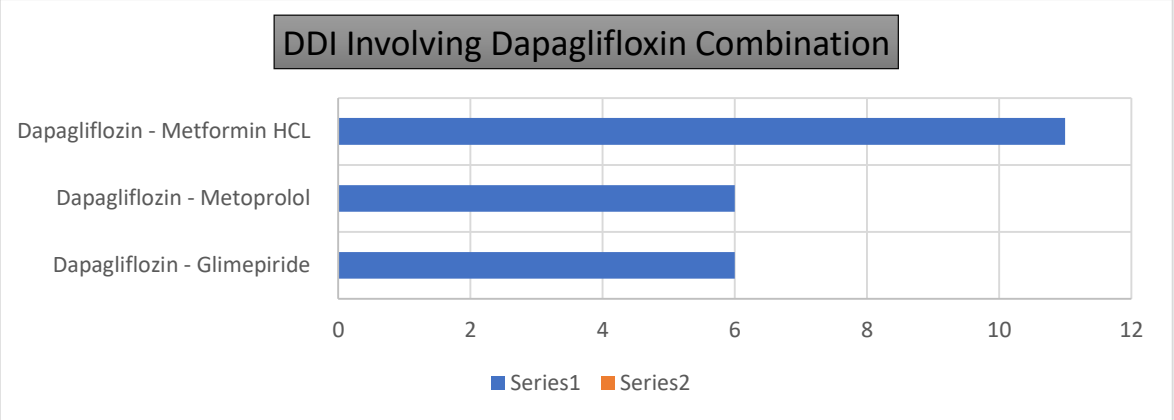
Dapagliflozin + Metoprolol and Dapagliflozin + Glimepiride both showed 6 interactions each.

Discussion :

The data indicates that dapagliflozin is most frequently co-prescribed with metformin HCL, resulting in the highest number of potential DDIs. This aligns with standard diabetes treatment practices but highlights the need for monitoring due to possible renal and metabolic effects.

The interactions with metoprolol and glimepiride, though less frequent, may increase risks such as hypoglycaemia or altered cardiovascular responses.

Fig. No. 04



These findings emphasize the importance of careful medication management in outpatient settings to minimize adverse effects while optimizing treatment outcomes.

5) Frequency of Drug combination with Metoprolol Succinate

"Frequency of Drug Combination with Metoprolol Succinate" shows the number of times metoprolol succinate was co-prescribed with three other medications in outpatient settings. The most frequent combination was with Metformin HCL (7 instances), followed by Naproxen and Prazosin HCL, each with 2 instances.

Metoprolol succinate is most commonly combined with metformin HCL, likely due to coexisting hypertension and diabetes in patients. While this combination is common, it may mask hypoglycaemic symptoms. The interactions with naproxen and prazosin HCL, though less frequent, raise concerns about increased hypotensive effects and renal risks, requiring careful monitoring.

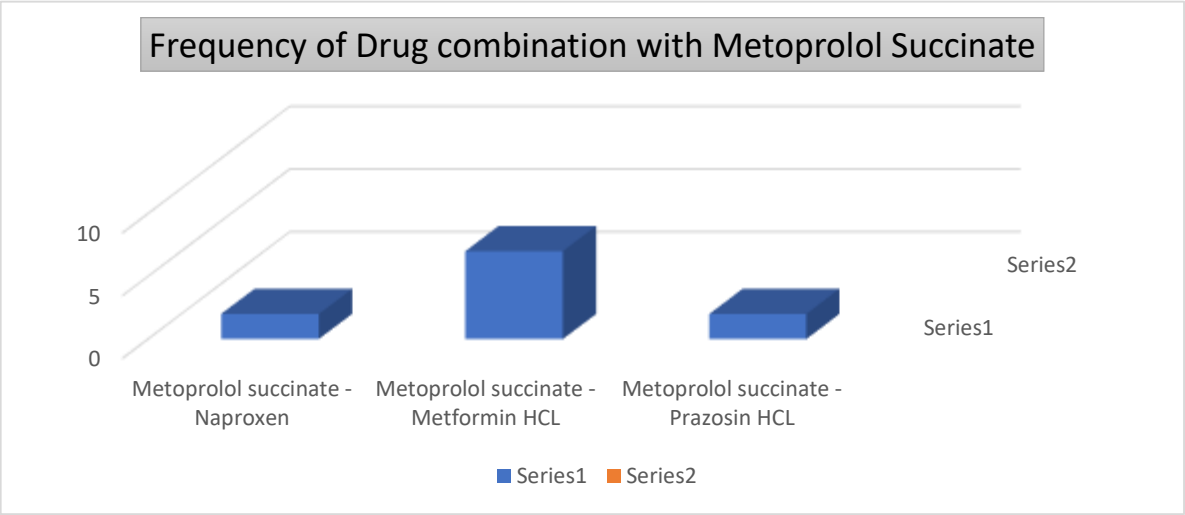


Fig. No. 05

Discussion :

Metoprolol succinate is most commonly combined with metformin HCL, likely due to coexisting hypertension and diabetes in patients. While this combination is common, it may mask hypoglycemic symptoms. The interactions with naproxen and prazosin HCL, though less frequent, raise concerns about increased hypotensive effects and renal risks, requiring careful monitoring.

6) Frequency of DDIs with Amlodipine Combination

"Frequency of DDIs with Amlodipine Combination" shows the interaction frequencies of amlodipine when co-prescribed with two other drugs. The combination of Amlodipine + Metformin HCL occurred 7 times, while Amlodipine + Clopidogrel occurred 3 times in the outpatient prescription data.

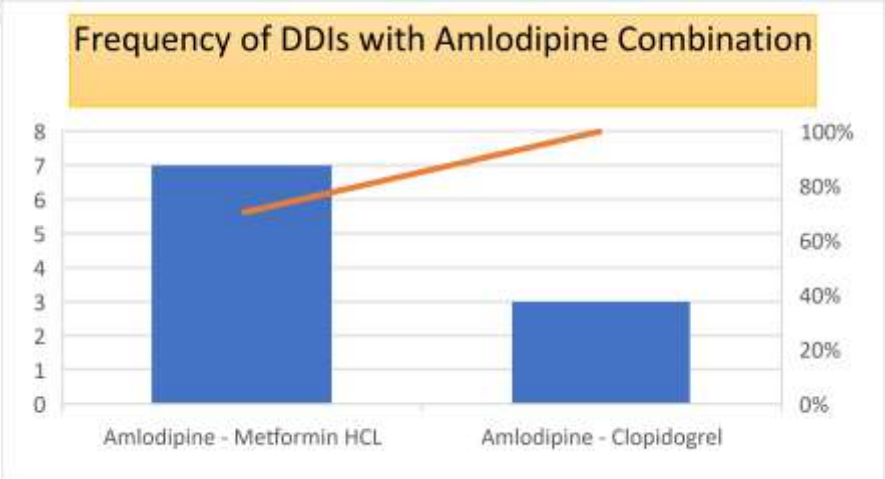


Fig. No. 06

Discussion :

Amlodipine was most frequently combined with metformin HCL, likely reflecting common co-management of hypertension and diabetes. This combination requires monitoring for potential metabolic or cardiovascular interactions. The combination with clopidogrel, although less frequent, may influence antiplatelet efficacy, especially in cardiovascular patients. These findings emphasize the need for awareness of DDIs in polypharmacy, especially in patients with chronic conditions.

Case Study:

Case Study 1:

CNS Depression Following Co-administration of Etizolam and Alprazolam in an Elderly Patient.

Abstract:

This case describes a clinically significant central nervous system (CNS) depressant interaction in an elderly patient who was co-prescribed etizolam and alprazolam. The patient developed excessive sedation and confusion, highlighting the need for cautious polypharmacy in geriatric populations.

Case Presentation:

A 65-year-old male with a medical history of hypertension, dyslipidaemia, anxiety disorder, and gastroesophageal reflux disease (GERD) had been prescribed the following medications:

Cilnidipine 10 mg (CILACAR) – once daily for blood pressure control

Rosuvastatin 10 mg + Aspirin 75mg (ROSEDAY A 10) – once daily for cardiovascular risk reduction

Etizolam 0.5 mg (UDAPA) – for anxiety symptoms

Pantoprazole + Domperidone (PANSA D) – for GERD management

Palmitoylethanolamide (PALMITOLE CAP) – for neuropathic pain/inflammatory support

Alprazolam 0.5 mg (TRIKA) – once at bedtime for sleep disturbances

A few days after initiating this regimen, the patient began experiencing excessive daytime drowsiness, confusion, and mild imbalance while walking. No other CNS depressants or alcohol use were reported. The symptoms raised concerns about a potential drug-drug interaction.

Management and Outcome:

Upon clinical evaluation, etizolam was discontinued, and the patient continued alprazolam at bedtime only. Over the following 3–4 days, the patient's symptoms of sedation and confusion gradually resolved, and gait stability improved. No further adverse events were reported on follow-up. (Shinoda J, 1999)[21]

Case Study 2:

Polypharmacy and Risk of Hypotension in an Elderly Diabetic with Cardiovascular Disease

Abstract:

This case illustrates the risk of additive pharmacodynamic effects from multiple antihypertensive agents in an elderly diabetic patient with established cardiovascular disease. The patient experienced symptomatic hypotension after being prescribed multiple agents with blood pressure-lowering potential.

Case Presentation: A 68-year-old male with a history of type 2 diabetes mellitus, hypertension, ischemic heart disease, and hyperlipidaemia was prescribed the following medications:

Glimisave M1 – Metformin + Glimepiride, for blood glucose control

Tendia 20 / Glyten 20 – Teneligliptin (DPP-4 inhibitor), for diabetes

Ecosprin AV 75/40 – Aspirin + Atorvastatin, for secondary prevention of cardiovascular events

Axcer 90 mg / Ticavic – Ticagrelor, a P2Y12 inhibitor for dual antiplatelet therapy

Nikorandil (Nikoran OD 10) – Anti-anginal agent

Ranolaz / Ran CV – Ranolazine, for chronic angina

Dytor Plus 5 – Torsemide + Spironolactone, for diuresis and heart failure management

Rexipra Plus / Curepam – Combination with likely antidepressant and anxiolytic effects

Pansa D / Panzel DM – Pantoprazole + Domperidone, for gastric protection

Isordil 5 mg SOS – Isosorbide dinitrate, for chest pain

Liquid Laxose / Dexluz – Laxative

TSF at night time – Likely a formulation for sleep (needs clarification)

The medications were prescribed for long-term use (mostly for 60 days).

Clinical Course:

Within a week of starting the new medication regimen, the patient reported episodes of dizziness, lightheadedness, and fatigue, especially when rising from bed or during prolonged standing. On clinical examination, the patient's blood pressure was found to be 92/60 mmHg, significantly lower than his baseline readings.

Management and Outcome:

After identifying the risk of polypharmacy-induced hypotension, the treating physician adjusted the dose of Dytor Plus to alternate days, and Nikorandil was withheld temporarily. The patient's blood pressure improved to 110/70 mmHg within a week, and symptoms resolved. (Mukai S, 2012)[22]

Case Study 3:

Risk of Bradycardia and Electrolyte Imbalance in a Geriatric Cardiac Patient with Polypharmacy

Abstract:

This case highlights the potential for adverse effects resulting from polypharmacy involving cardiovascular agents, including bradycardia and hyponatremia, in an elderly patient with multiple comorbidities.

Case Presentation:

A 72-year-old male with a known history of congestive heart failure, atrial fibrillation, type 2 diabetes, and hypertension was under long-term treatment and presented for routine follow-up. His prescription included the following medications:

Glimy 1 – Glimepiride for type 2 diabetes

Lanoxin 0.25 mg – Digoxin, prescribed 5 times weekly for atrial fibrillation

Isoptin SR 120 mg – Verapamil (calcium channel blocker)

Cordarone 100 mg – Amiodarone, an antiarrhythmic

Dytor 40 – Torsemide, a loop diuretic

Hyponat 15 – Tolvaptan, a vasopressin antagonist

Azmarda 50 / Neptaz 50 – Sacubitril/valsartan, for heart failure

Omez 40 / Acitab XL – Proton pump inhibitor

Ankool SF / Racijraft – Antacid + mucosal protectant

B Protin Powder – Nutritional supplement

Most of these medications were prescribed for a 60-day course, with multiple medications administered once or twice daily.

Clinical Course:

Two weeks after starting this regimen, the patient presented with episodes of lightheadedness, confusion, and general weakness. Clinical examination revealed a heart rate of 48 bpm and serum sodium level of 124 mEq/L.

Management and Outcome:

Digoxin and Verapamil were temporarily withheld. The dosage of Tolvaptan was re-evaluated and tapered. Electrolyte imbalance was corrected with fluid and electrolyte management. After adjustments, the patient's heart rate normalized to 62 bpm and serum sodium improved to 134 mEq/L within 5 days. (Bhatia N, 2021)[23]

Conclusion:

This retrospective study provides clear evidence that drug-drug interactions (DDIs) are prevalent and clinically significant in outpatient prescriptions, especially in patients with chronic conditions requiring polypharmacy. The most common and severe interactions were observed with combinations involving antidiabetic agents (e.g., metformin, glimepiride, dapagliflozin), antihypertensives, and antiplatelet medications like aspirin and clopidogrel. These interactions, if not identified and managed properly, can lead to adverse outcomes such as hypoglycaemia, bleeding, or reduced therapeutic efficacy.

The findings reinforce the importance of implementing standard DDI screening tools during prescription and dispensing processes. Clinicians must remain vigilant and regularly update their knowledge on drug interactions, while pharmacists should actively participate in cross-checking prescriptions to ensure safety. Education, digital alerts, and interprofessional collaboration can collectively minimize DDI risks.

Ultimately, early identification and prevention of DDIs not only protect patient health but also reduce healthcare burdens caused by avoidable complications, hospitalizations, and prolonged treatments. This study emphasizes the urgent need for integrated, proactive approaches in managing DDIs in outpatient care.