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# Pharmacokinetic drug-drug interaction and their implication in clinical management

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## Abstract

The Drug-drug interactions (DDIs), which have a prevalence of 20–40% in developed nations and are particularly common in the elderly due to polytherapy. Particularly, poly-therapy raises the bar for therapeutic control and, thus, the danger of clinically significant DDIs, which can both lead to the emergence of adverse drug responses and lower clinical efficacy. The two primary categories of DDIs are pharmacokinetic and pharmacodynamics. In this review, we searched articles published using the Reference lists. We described the mechanism of pharmacokinetic DDIs with a focus on their clinical implications.

**Keywords:** Absorption, adverse drug reaction, distribution, drug-drug interactions, excretion, metabolism, poly-therapy.

## INTRODUCTION

When a second drug is used concurrently with a first drug, a drug-drug interaction takes place (Magro et al., 2012). They are a significant contributor to hazardous medication reactions.reactions that are largely avoidable and predictable. (Seymour, R. M., and Routledge, P. A. (1998).Even so, their prevention is still difficult.As the number of medications that could potentially be used in clinical practise interactivity is high.Additionally, it seems challenging to employ the methods for identifying interactions-at-risk coprescriptions and codispensings in clinical and official practise (van der Sijs et al., 2016).Zheng et al., 2018; Payne et al., 2015). According to According to studies, DDIs account for 2-5% of hospital admissions.among individuals above the age of 65 (Becker et al., 2007; Olivier et al., 2009;hospital admissions (Bénard-Laribière et al., 2015), and 1% in the population at large (Dechanont et al., 2014).Currently, an increasing segment of the population is older and presenting with chronic conditions as a result of demographic and epidemiological changes.Having comorbidities that are ongoing (Global Burden of Disease Study, 2015). The ageing of the population is anticipated to have significant a high rate of polypharmacy, drug usage, and a long-term use of many medications (Haider et al., 2007; Nobili et al., 2011;2014 Maher et al) .The World Health Organization describes polypharmacy as "the administration of numerous medications at the same time or the administration of an excessive number of pharmaceuticals," and ongoing polypharmacy is confined to prescription drugs.taken frequently and for a long time(Fincke et al., 2005).The latter being the key risk element for DDIs, it is

likely that the risk represented by the population's exposure if these harmful drug linkages continue to grow in the future,Unless focused actions are successful in containing it (Guthrie et al., 2015;Stoll and Kopittke, 2015).

Drug-drug interactions (DDIs) are one of the most prominent reasons for ADRs, and we found that the elderly are more likely to experience these manifestations because of polytherapy. [4,5,6,7] In reality, polytherapy increases the complexity of therapeutic management, increasing the possibility of clinically significant medication interactions that can lead to the development of adverse drug reactions (ADRs) and either decrease[8,9] or boost clinical efficacy. [10,11].The patient is at risk of developing additional adverse drug reactions (ADRs) as a result of the "prescribing cascade," which takes place when an ADR is misunderstood and new, perhaps unneeded medications are given. [12]

DDI can be divided into two categories:

1. Pharmacokinetic: Consists of the processes of absorption, distribution, metabolism, and excretion, each of which is connected to either treatment failure or toxicity;

2.Three subgroups of pharmacodynamics can be identified: (1) direct effect on receptor function, (2) disruption of a biological or physiological regulatory mechanism, and (3) additive or counterproductive pharmacological action.

In this review, we discussed the therapeutic relevance of pharmacokinetic DDI while drawing the reader's attention to additional original and review studies that discuss pharmacological interactions.

**Absorption**

There are many potential mechanisms to affect drug absorption, some of which are hypothetical, such as: gastrointestinal motility;

gut pH;

drug Solubility;

Gut physiology;

Intestinal bacteria;

Activity of protein transporters.

Drug adsorption is one method of action. This happens when a drug gets adsorbed onto a binding agent, which makes it harder for the drug to be absorbed into the blood.May not be therapeutically useful. Antibiotics containing tetracycline polyvalent metal cations (such as iron, aluminium,Or calcium as located in antacids) causes a reduction in tetracycline levels in the blood (8).Warfarin, an oral anticoagulant, and bile acids are all bound by cholestyramine, an anionic binding resin.This compound lessens the drug’s hypoprothrombinemic and mean plasma warfarin concentrations (9).

Medication-induced changes in gastrointestinal motility may affect how a drug is absorbed. The small intestine is where most medications are largely absorbed. Reducing or Accelerating the rate at which the medication enters this region.The digestive system could alter or boost the Medication absorption rate.Drug transit times may be prolonged by peristalsis-depressing medications (such as opioids like morphine and anticholinergics like atropine). Extending the time for digestion in the gut Absorption. Metoclopramide is a prokinetic drug that may promote stomach empting, which would increase how quickly a medication is absorbed.

Some medications’ ability to be absorbed can be changed by altering the pH of the digestive system. Some medications must dissolve in an acidic or basic environment.In a non-ionized medium, weak acids would more easily exist.(i.e., form that is lipid-soluble) in an acidic environment, so while weak bases are more easily absorbed.Would be more absorbable in an uncomplicated setting.Drugs like ketoconazole and itraconazole, which are antifungal medications, may have less absorption when used with medications that raise gastric pH, such as proton pump inhibitors and antacids.An acidic environment promotes absorption (10) .

Drug bioavailability may be impacted by interactions between foods and medications. Most medications have a correlation between their action and bioavailability. Drug-food interactions can alter the drug bioavailability via a chemical process like a physiological reaction to food intake or through chelation.Changes in bile and stomach acidity would be examples of this.Gastrointestinal motility and secretion. Food–drug interactions that just change how quickly a medication is absorbed are prevalent, but infrequently have clinical significance (11).

**Modulation of P-glycoprotein (P-gp) intestinal**

P-gp, also known as gp-120 for its molecular weight, is a transmembrane protein that is encoded by the human multidrug resistance gene-1 and is a member of the ABC superfamily, along with the other 41 members arranged into 7 families (A to G). [23] P-gp plays a protective role by influencing the trans membrane drug diffusion by being present in the liver, pancreas, kidney, small and large intestine, adrenal cortex, testes, and leukocytes. This influences the absorption, excretion, and tissue distribution of the drugs (i.e., central nervous system, foetal and gonadic tissues). [24]

P-gp controls medication absorption in the intestine (it is found on the luminal surface of enterocytes) and encourages drug excretion (it is present on the side tubular of epithelium renal and biliary side of hepatocytes). As a result, the use of medications that can either stimulate or inhibit P-gp function can result in the development of DDI.The bioavailability of medications that are ineffectively absorbed can be greatly increased by P-gp inhibition. [25]

The effects of terfenadine on the transport of doxorobucin as well as those of chlorpromazine and progesterone on the transport of cyclosporine should be mentioned among the interactions examined at the time of this study. [26] If digoxin, theophylline, or anticancer medications are co-administered with macrolides (such as erythromycin, roxithromycin, or clarithromycin), PPIs (such as omeprazole or esomeprazole), or anti-arrhythmic medications, the DDIs on P-gp may cause a clinical impact (e.g., dronaderon, amiodarone, verapamil or diltiazem).

Cytochrome P450 (CYP) isoform 3A4 also metabolises a number of pharmaceuticals that are carried by P-gp, but not all of them (for example, cyclosporine, antiepileptic medications, antidepressants, fluoroquinolones, quinidine, and ranitidine), which might make it difficult to interpret interactions (see later).Therefore, co-administration of these medications with the aforementioned recognised P-gp inhibitors causes a clinically obvious DDI.

Aripiprazole and its active metabolite, dehydroaripiprazole, but not risperidone, paliperidone, olanzapine, or ziprasidone, are recently reported to be potent P-gp inhibitors in vitro. However, in vivo, the administration of these drugs is unlikely to cause DDIs at the blood-brain barrier; however, the possibility of DDIs in the intestine should not

It Is crucial to stress that a DDI may also be used for clinical management. Shi et al.'s[27] documentation that sildenafil decreases P-transporter gp's function actually suggests a viable tactic for boosting the distribution and perhaps even the efficacy of anticancer medications.

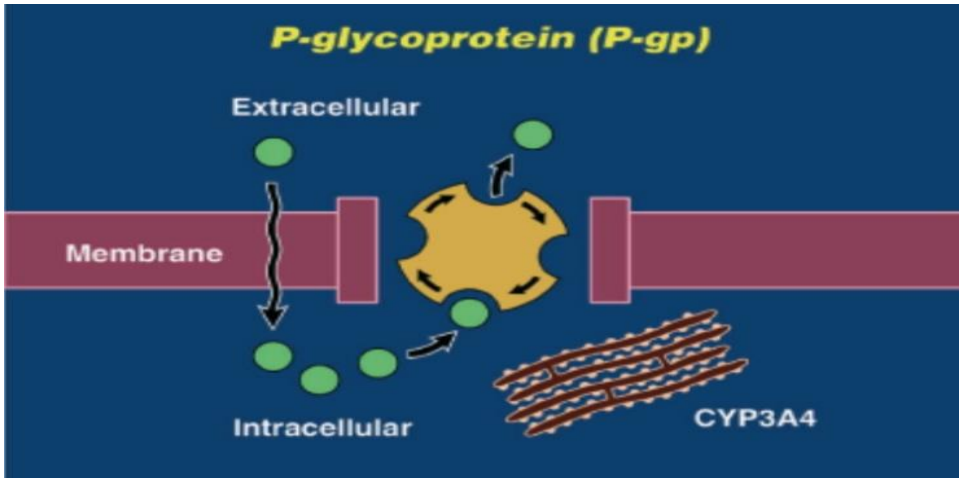


**Fig. 1. P-glycoprotein carrier system.**

# DISTRIBUTION

Drugs are typically delivered through binding to proteins in the plasma and tissues. The three most significant plasma proteins that interact with medicines are albumin, 1-acid glycoprotein, and lipoproteins. Basic medications are typically more extensively bound to lipoproteins, albumin, or both, whereas acidic drugs are typically more extensively bound to 1-acid glycoprotein, albumin, or both. The concentration of the drug at the active site and hence its efficacy are typically determined by unbound drug, which is only available for passive diffusion to extravascular or tissue locations.The most abundant protein in plasma is albumin, which is produced in the liver and found in plasma as well as extracellular fluids found in the skin, muscles, and other tissues. The concentration of albumin in intestinal fluid is roughly 60% lower than that in plasma. Since albumin has five binding sites (for tomoxifen, digoxin, bilirubin, benzodiazepines, and warfarin, respectively), sites I and II are the most well-known. [28].

Site II is known as the benzodiazepine-binding site, and it is located in subdomain IIIA. Site I, also referred to as the warfarin binding site, is formed by a pocket in subdomain IIA[29]. Drug probes for site II that are specific include ibuprofen and diazepam. [29,30,31] [Table 1]

**Table 1**

Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin

| Site I (warfarin) | Site II (benzodiazepines) |
|---|---|
| Chlorothiazide | Ketoprofen |
| Phenytoin | Ibuprofen |
| Glibenclamide | Indomethacin |
| Naproxen | Dicloxacilline |
| Salicylates | Nimesulide |
| Nimesulide | |
| Diclofenac | |
| Sulphamidics | |
| Fluoroquinolones | |
| Valproate | |

Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin.

Other molecules dissolve into solution to reach the site of action while the free molecules engage with their molecular targets and are digested. The ratio of bound drug concentration to free drug concentration, which measures the extent of plasma protein binding, varies widely between drugs and can potentially reach very high levels, especially when it is larger than 0.9; otherwise, it is regarded as low (0.2). High plasma protein binding affinity drugs may be more susceptible to being replaced by drugs with higher affinity for the same binding location.From a purely clinical standpoint, that displacement may be linked to symptoms, side effects, or toxicities if the substitute medicine has a higher affinity for plasma proteins (>90%), a smaller volume of distribution, a narrower therapeutic range, and a quicker beginning of action.

When warfarin and diclofenac are taken together, a typical pharmacological displacement can be seen. Because diclofenac and warfarin have a similar affinity for albumin, when it is given to a patient who is taking warfarin on a long-term basis, the warfarin is dislodged from its binding site. Serious hemorrhagic responses emerge as free warfarin concentrations in the plasma rise.

# Drug metabolism

Metabolism, another name for biotransformation, is blossoming with new knowledge. According to recent investigations, the most clinically significant medication interactions involve metabolic pathways. The majority of

medicines are at least partially removed from the body through being a substance that is less lipid-soluble due to chemical change. Those are excreted and not reabsorbed over a lipid membrane in the bile or by the kidney. While metabolism happens throughout the body, including in the skin, lungs, intestines, and plasma, the majority of metabolism takes place in the hepatocyte's smooth endoplasmic reticulum.Briefly, there are two phases to metabolism. (Fig. 3 and Fig. 4) Metabolic phase I includes the a drug's oxidation, hydrolysis, or reduction. These processes make the drugs more water soluble and make it easier for the body to get rid of them. Stage II metabolism necessitates the joining of an additional adding a chemical to the medication to produce an inactive chemical and a medication that is more water soluble. Stage II glutathione conjugation, glucuronidation, sulfation, acetylation, and methylation are among the processes.

The hepatic CYP is the enzyme responsible for this reaction's catalysis. Iron, heme, and a protein complex make up CYP. NADPH and molecular oxygen are used.Using (a reduced version of NADP) as an electron source, this a number of oxidations are catalysed by the cytochrome system.Oxidised medication is produced as a result of reduction processes.product (25). (25). Even if there are over 50 different just three families of enzymes have been found.The CYP1, CYP2, and CYP3 enzymes are in charge of the most substances, including steroid

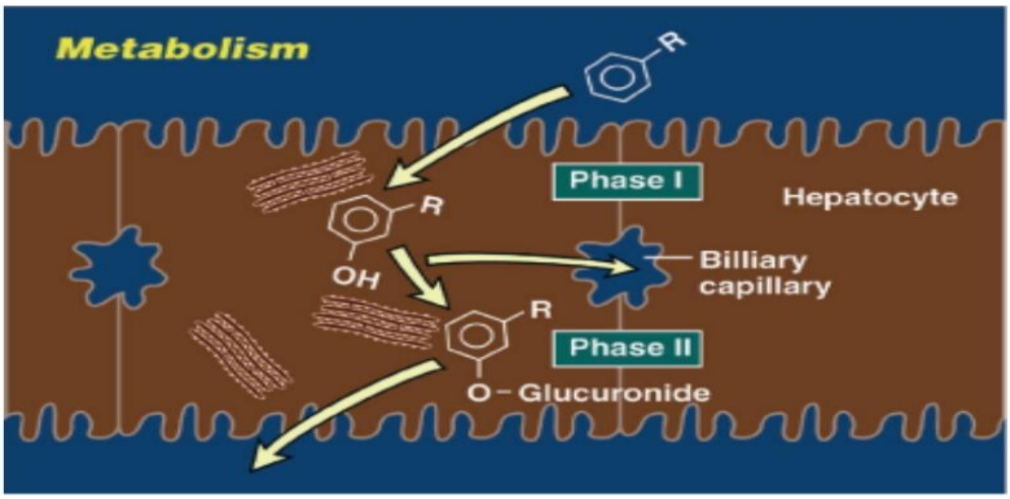


**Fig. 3. Phase I and II metabolism.**

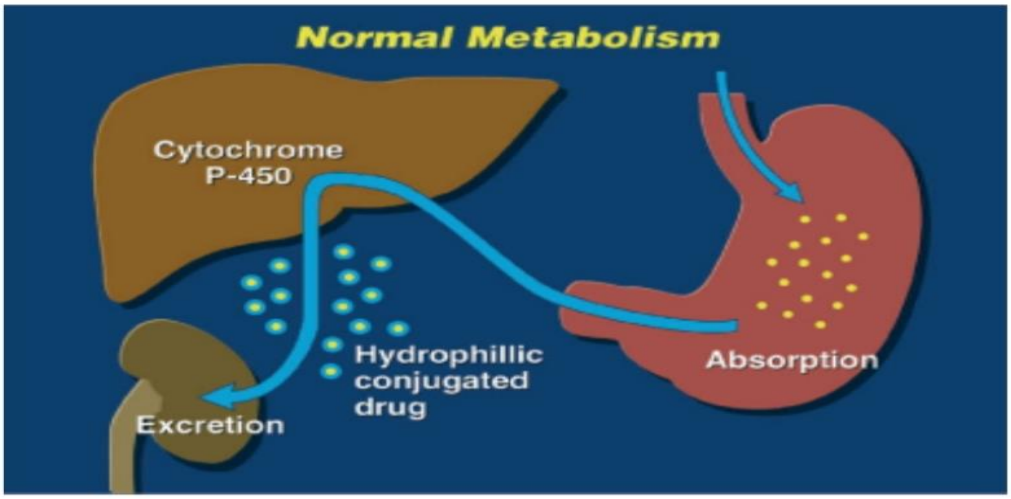


**Fig. 4. Normal metabolism.**

metabolism,vitamins, prostaglandins, other endogenous compounds, and a wide range of medications. Each family's subfamilies are identified by a capital letter, and each enzyme's name ends in an Arabic number. Consequently, the unique enzymes CYP2C9 and CYP2C19 is a member of the CYP2 family, as well as theCYP2C family. Any two

medications that are processed by the same enzyme theoretically have the potential to interact with one another.Both medications would fight for the same enzyme.When one drug is metabolised, the second drug may not. Metabolism decreased, raising blood levels as a result of the unmetabolized medication. To prepare for a clinically substantial CYP system-related medication interaction. It's important to familiarise yourself with the substrates,the isoenzymes' inducers and inhibitors.The substance that is known to be digested by the isoenzyme is referred to as the "substrate." An inhibitor is a indicates a medicine known to compete with or interfere with the isoenzyme, whereas the word "inducer" refers to a substance that quickens a substrate's metabolism.

# Drug excretion

The kidneys, liver, lungs, faeces, perspiration, saliva, and milk are the organs and means of drug excretion (elimination). Although the excretion through milk is crucial when the medicines can reach the baby during nursing, the excretion through saliva, perspiration, and lungs (for volatile medications) has minimal quantitative relevance.

Drug excretion occurs mostly through:

1. Kidney tubular excretion (glomerular filtration, tubular reabsorption and active tubular secretion)
2. Biliary excretion.[83]

The drug's elimination from the body can experience a variety of interactions while being excreted in this organ by another substance. [84] The organ in charge of eliminating medicines and their metabolites is the kidney. When two or more medications use the same transport route at the level of active tubular secretion, the interaction may happen due to a process of competition. NSAIDs serve as an illustration of how methotrexate toxic effects manifest when renal excretion of the anti-proliferative medication is inhibited. [85] Amoxicillin was shown to reduce methotrexate's renal clearance as well. [86] The area under the AUC of oseltamivir is increased by 2.5 times by probenecid, a powerful inhibitor of the anionic route of renal tubular secretion. [87]However, this rivalry between medications can be used in a therapeutic way. Probenecid, for instance, can raise the serum content of cephalosporins and penicillins, delaying their renal elimination and reducing dosage requirements. Probenecid actually works by blocking an organic anion transporter in the renal tubules by competitive inhibition, which raises the plasma concentrations of other transporter substrates while decreasing excretion. [88] Several medications have the ability to obstruct tubular transit. Particularly, the tubular secretion of many substances may be influenced by the H2 receptor inhibitor cimetidine. Its impact on human organic cation transporters (hOCT1 and hOCT2) and human multidrug and toxin extrusion (hMATE1 and hMATE2-K) could change the serum levels of other drugs despite normal renal function. [89]

In vitro research has also shown that PPIs, such as omeprazole, pantoprazole, lansoprazole, rabeprazole, and tenatoprazole, are strong hOCT-inhibitors and may influence metformin transport. [90] The clinical applicability of these DDIs may be clarified, though. Additionally, the interactions may take place during tubular reabsorption. When present in the urine as ions, many medicines move through tubular cells via diffusion. The pharmacologically induced variations in urine pH have an impact on the degree of ionisation of some medications and may therefore have an impact on the re-absorption from the renal tubule. [91]Acidic medications are less likely to be absorbed if the urine's pH is alkaline, whereas basic pharmaceuticals are less likely to be absorbed if the pH is acidic.The pKa of the medicine, or the pH at which 50% of the molecules in solution are present in ionised form, must be between 7.5 and 10.5 for bases and between 3.0 and 7.5 for acids for the changes in urine pH to be of practical significance.

The degree of the drug's dissociation can actually fluctuate noticeably depending on the pKa levels. Due to their ability to alter urine pH, substances including ammonium chloride, tromethamine, and diuretics may have an impact on how many acidic and basic medicines are excreted[15], and this interaction may be employed to speed up drug elimination from the body. On the other hand, the patient may still have side effects from the interaction of diuretics and lithium salts.Changes in serum sodium levels have an impact on the excretion of lithium, a monovalent cation. As a result, prolonged use of some diuretics, such as thiazides, may cause a high excretion of sodium, which may increase the re-absorption of lithium and result in substantial toxic consequences from relative overdosage. [92,93]

Some highly ionised acidic and basic medications are actively transported by the epithelium of the renal tubule. The presence of the transporter, a protein that permits the transfer through cellular membranes, determines how quickly molecules are transferred. Since two medications can complete each other up to the saturation of the transporter's capacity when they are substrates of the same transmembrane transporter, At that point, the elimination rate begins to converge toward a zero order (saturable) process.

# CONCLUSIONS

DDIs are a frequent clinical issue while treating patients with a variety of medications. Even if this clinical relevance is connected to the pharmacology of each drug, it should be noted that just two substances can cause the development of a DDI. A DDI can actually cause a clinically significant effect when there are medications present that have a low therapeutic index, a long half-life, and a higher binding to plasma proteins.

The development of DDI Is a problem with a particular medicine, not a class of drugs, and this concern can be underestimated if we only take the SPC into account