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Various Mechanisms of Pharmacokinetic drug-drug interaction: A Comprehensive Review

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Abstract
With a prevalence of 20 - 40%, drug-drug interactions (DDIs) are one of the most frequent reasons for medication errors in industrialised nations, especially in older patients undergoing polytherapy. Specifically, poly-therapy raises the possibility of clinically significant drug-drug interactions (DDIs) and hence the complexity of therapeutic management. DDIs can cause adverse medication responses or decrease clinical effectiveness. The two primary categories of DDIs are pharmacokinetic and pharmacodynamic. In this study, we analysed the articles published up to 30th June 2023; using Medline, PubMed, Embase, and the Cochrane library. We then explained the mechanism of pharmacokinetic DDIs, with an emphasis on their clinical implications.

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

I. Introduction
By identifying and measuring the risks connected to medication usage, pharmacovigilance, also known as post-marketing monitoring, seeks to improve knowledge of the key elements of adverse drug reactions (ADRs) and the pathogenic processes behind them [1]. In fact, adverse drug reactions (ADRs) are a prevalent clinical issue that may contribute to an increase in the quantity and length of hospital stays [2, 3]. One of the most frequent causes of adverse drug reactions (ADRs) is drug-drug interactions (DDIs), and we have shown that polytherapy frequently results in these manifestations in the elderly [4 - 7]. In actuality, poly-therapy makes therapeutic management more difficult and raises the possibility of clinically meaningful medication interactions, which can lead to the development of adverse drug reactions (ADRs) and either decrease or boost clinical efficacy [8 - 11]. The "prescribing cascade," which happens when an ADR is misinterpreted and other, possibly needless medications are given; as a result, the patient is at risk of developing more ADRs, may be identified by polytherapy [12].

DDIs are divided into two primary categories:

1. **Pharmacokinetic -** Involves the processes of excretion, metabolism, distribution, and absorption—all of which are linked to toxicity or therapeutic failure.
2. **Pharmacodynamic -** Can be broken down into three smaller groups: (1) direct impact on receptor function; (2) disruption of a physiological or biological regulatory mechanism; and (3) additive/opposed pharmacological action.

We reviewed the pharmacokinetic DDI mechanism in this review, emphasising its clinical consequences and drawing the reader's attention to additional original and review studies regarding pharmacological interactions.

II. Materials and Methodology
We searched the following databases: Medline, PubMed, Embase, Cochrane library, Reference lists, and ADR, medication interactions, polytherapy, and elderly. The search was conducted till 30th June 2023.

Pharmacokinetic DDI - Pharmacokinetic interactions are found by monitoring changes in serum drug concentrations and the clinical symptoms of the patient. They are frequently evaluated based on each medication's specific knowledge. They were engaged in every step of the processes that will now be discussed, from absorption to excretion, as previously stated.

Absorption

Gastro-intestinal absorption - A number of medications with functional action on the digestive system and the complexity of the gastrointestinal tract provide ideal conditions for the establishment of DDI, which may change the bioavailability of

medications [13]. The way a medication is absorbed via the gastrointestinal mucosa can be influenced by a number of factors. The shift in stomach pH is the primary cause. Most medications taken orally need a stomach pH in the range of 2.5 - 3 to dissolve and be absorbed. As a result, medications that rise stomach pH; such as antacids, anticholinergics, proton pump inhibitors (PPI), or H_2-antagonists, might alter how other medications work when taken together. Cefpodoxime bioavailability is actually decreased by H_2 antagonists (like ranitidine), antacids (like aluminium hydroxide and sodium bicarbonate), and proton pump inhibitors (like omeprazole, esomeprazole, and pantoprazole) that raise the pH of the stomach. However, these medications also make it easier for beta-blockers and tolbutamide to be absorbed. Furthermore, because antifungal treatments (such ketoconazole or itraconazole) need an acidic environment to dissolve well, co-administering them with medications that might raise stomach pH may result in a reduction in the antifungal drugs' ability to dissolve and absorb [14]. Therefore, at least two hours after the administration of antifungal medicines, antacids, anticholinergics, or PPIs may be given [15]. Similarly, it is not advised to administer medications that might raise the pH of the stomach, such as ampicillin, atazanavir, clopidogrel, diazepam, methotrexate, vitamin B12, paroxetine, and raltegravir. On the other hand, ingesting medications that lower stomach pH (such pentagastrin) may have the opposite effect. It is important to remember that the degree of delayed drug reactions (DDIs) brought on by changes in stomach pH is mostly determined by the medication's pharmacodynamic properties, namely its limited therapeutic range. Complex formation is another aspect that alters medication absorption. In this instance, poorly absorbed complexes can be formed when tetracyclines (such doxycycline or minocycline) in the digestive system react with metal ions (including calcium, magnesium, aluminium, or iron). As a result, several medications can drastically lower the absorption of tetracyclines, such as antacids, preparations containing magnesium salts, and preparations containing calcium and iron [16]. Similarly, since the metal ions in antacids combine with the drugs to create complexes, they reduce the absorption of tetracyclines, penicillamines, and fluoroquinolones (like ciprofloxacin). Antacids and fluoroquinolones should be taken at least two hours apart, according to observations [17, 18]. The digestive system cannot absorb bile acids due to the binding of cholestyramine and colestipol, but they can also bind other medications, particularly acidic medications (e.g., warfarin, acetyl salicylic acid, sulfonamides, phenytoin, and furosemide). As a result, the time gap between the administration of colestipol or cholestyramine and other medications may be as long as feasible, ideally four hours [20]. Third component influencing the absorption of DDIs is motility problems. Metoclopramide, cisapride, cathartic, and other medications that can speed up stomach transit can also shorten the time a drug spends in touch with the mucosal region of absorption, which can result in less drug absorption (entero-protected or controlled-release formulations) [21]. Metoclopramide, for instance, can speed up stomach emptying and reduce the absorption of digoxin and theophylline while speeding up the absorption of levo-dopa, acetylsalicylic acid, alcohol, acetaminophen, and tetracycline [22]. Lastly, levodopa and metildopa's absorption might be inhibited by iron.

Modulation of P-glycoprotein (P-gp) intestinal - P-gp, often known as gp-120 due to its molecular weight, is a transmembrane protein that is part of the adenosine triphosphate-binding cassette (ABC) superfamily along with 41 other members that are categorised into 7 families (A to G). It is encoded by the human multidrug resistance gene-1 [23]. P-gp is found in the liver, pancreas, kidney, small and large intestine, adrenal cortex, testes, and leukocytes. It plays a protective role by influencing the diffusion of trans membrane drugs, which lowers or increases their absorption or restricts their distribution across tissues (such as the central nervous system and the tissues of the foetus and gonads) [24]. P-gp is expressed on the luminal surface of enterocytes, where it controls intestinal absorption of pharmaceuticals. It is also present on the tubular side of the renal epithelium and the biliary side of hepatocytes, where it facilitates drug excretion. As a result, the administration of medications that might stimulate or inhibit P-gp function can cause DDI to occur. Drugs that are poorly absorbed can have their bioavailability greatly increased by P-gp inhibition [25]. The effects of terfenadine on doxorobucin transport as well as the effects of progesterone and chlorpromazine on cyclosporine transport are noteworthy among the interactions that were investigated at the time of this study [26]. The co-administration of DDIs on P-gp with macrolides (such as erythromycin, roxithromycin, or clarithromycin), PPIs (such as omeprazole or esomeprazole), or anti-arrhythmic medications (such as dronaderon, amiodarone, verapamil, or diltiazem) may result in a clinical effect when these medications have a low therapeutic index. The cytochrome P450 (CYP) isoform 3A4 metabolises many (but not all) of the medicines carried by P-gp, including cyclosporine, antiepileptic medications,

antidepressants, fluoroquinolones, quinidine, and ranitidine. This might complicate the interpretation of interactions between pharmaceuticals. Consequently, a clinically noticeable DDI is produced when these medications are used concurrently with the previously mentioned recognised P-gp inhibitors. Aripiprazole and its active metabolite, dehydroaripiprazole, have recently been reported to be potent P-gp inhibitors in vitro; however, risperidone, paliperidone, olanzapine, and ziprasidone do not exhibit this property. In vivo, the administration of these medications is unlikely to cause DDIs at the blood-brain barrier, but it is not ruled out that DDIs could occur in the intestine. It is crucial to emphasise that a DDI may be applied to clinical treatment as well. Indeed, sildenafil suppresses P-gp's transporter function, as reported by Shi et al. [27]. This finding raises the possibility of a new tactic to improve anticancer medication distribution and maybe activity.

Distribution - Typically, medications are transferred by binding to tissues' proteins and plasma. The most significant plasma proteins that interact with medications include lipoproteins, α1-acid glycoprotein, and albumin. Medicines that are acidic tend to bind more tightly to albumin, whereas basic medicines tend to bind more tightly to lipoproteins, α1-acid glycoprotein, or both. The only medication that may passively diffuse to extravascular or tissue locations is unbound medication, which usually controls drug concentration and, consequently, effectiveness at the active site. The most abundant protein in plasma is albumin, which is produced in the liver and found in extracellular fluids found in the skin, muscles, and other tissues in addition to plasma. The concentration of albumin in intestinal fluid is around 60% that of plasma. Digoxin, bilirubin, warfarin, benzodiazepines, and tomoxifen are among the five binding sites for albumin; nevertheless, sites I and II are the most well-characterized [28]. A pocket in subdomain IIA forms site I, also referred to as the warfarin binding site [29], while site II, which is found in subdomain IIIA, is referred to as the benzodiazepine-binding site. Two specific drug probes for site II are ibuprofen and diazepam [29 - 31].

Site I (Warfarin)	Site II (Benzodiazepines)
Chlorothiazide	Ketoprofen
Phenytoin	Ibuprofen
Glibenclamide	Indomethacin
Naproxen	Dicloxacilline
Salicylates	Nimesulide
Nimesulide	
Diclofenac	
Sulphamidics	
Fluoroquinolones	
Valproate	

Table – 1: Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin

Other molecules enter solution to reach the site of action as the free molecules interact with and are metabolised by their molecular targets. The ratio of bound drug concentration to free drug concentration, which represents the degree of plasma protein binding, can vary significantly across medications and potentially reach very high levels. It is deemed low (<0.2) if the ratio is less than 0.9. It is possible that drugs having a higher affinity for the same binding site will displace those with a higher degree of plasma protein binding. From a purely clinical perspective, the displacement of a drug may result in symptoms, toxicities, or side effects if the drug has a narrow therapeutic index, a reduced volume of distribution, a higher degree of binding to plasma proteins (>90%), and a faster onset of action. Combining warfarin with diclofenac might result in a typical pharmacological displacement. Due to their similar affinity for albumin, diclofenac and warfarin cause the latter to be displaced from its binding site when given to a patient on a long-term warfarin treatment. Serious hemorrhagic responses arise from an increase in the plasma concentration of free warfarin.

Metabolism - Many different medications undergo biotransformation, with the CYP enzyme family having a major influence. About half of the thirty CYP isoforms found in families 1-4 in humans are in charge of drug metabolism; however, only six of these isoforms, which are members of families CYP1, 2, and 3, namely CYP1A2, 3A4, 2C9, 2C19, 2D6, and 2E1, are primarily engaged in hepatic drug metabolism [32 - 35]. The multitude of medications that experience CYP-mediated oxidative biotransformation is the cause of the majority of clinically noteworthy drug interactions in the context of multiple medication treatment. Numerous DDIs have anything to do with CYP enzyme stimulation or inhibition.

Inhibition - The majority of DDIs that are clinically useful are inhibition-based. In this mechanism, a medication's direct contact with an enzyme reduces its activity. This interaction typically starts with the inhibitor's first dosage, and the inhibition's eventual extinction is correlated with the half-lives of the drug [36,37]. Basic processes determine the clinical consequences of metabolic inhibition, which can be either irreversible or reversible (competitive, metabolic-intermediate complex, non-competitive).

Reversible inhibition

Competitive - When the inhibitor and substrate vie for the same binding site on the enzyme, competitive inhibition takes place. The inhibitory mechanism in this kind of contact is direct and quickly reversible. The medications are transformed into nitroso-derivatives, which bind to the reduced form of CYP enzymes with a high affinity, through a series of CYP dependent stages. As a result, CYP enzymes cannot be further oxidised. The only way to restore function is to synthesise new enzymes, which may take several days [38]. It is dependent upon the relative concentrations of each species as well as the substrate-versus-inhibitor binding constant ratio. Azole antifungal medications, certain HIV protease inhibitors like nelfinavir mesylate, and antihypertensives like diltiazem are among the CYP3A4 inhibitors that function through this method of inhibition [39, 40]. Metoprolol dosage reduction during co-administration is recommended due to the documented two-fold reduction in oral clearance of the drug in the presence of propafenone [41]. On the other hand, few researchers recently published a case study of an 85-year-old lady who experienced psychomotor agitation and visual hallucinations while receiving venlafaxine and propafenone therapy [42]. Since propafenone is a recognised substrate and inhibitor of both CYP2D6 and P-gp, and venlafaxine is metabolised largely by CYP2D6; researchers hypothesised a DDI between the two drugs. Consequently, the development of hallucinations may be accompanied with a rise in venlafaxine plasma concentrations caused by propafenone. Combining the administration of omeprazole and diazepam (CYP2C19), fluoxetine and desipramine (CYP2D6), thioridazine and propranolol (CYP2D6) [45 - 47], tolbutamide and phenytoin (CYP2C9) [48], and diltiazem and cyclosporin (CYP3A) results in similar DDI [49 - 51]. The CYP2C19 inhibitor omeprazole reduces the antiplatelet effect of clopidogrel by preventing the drug's biotransformation into its active metabolite [52]. This interaction is linked to a 27% higher risk of mortality or readmission in individuals hospitalised for acute coronary syndrome [53]. Comparatively, etravirine's suppression of CYP2C19 may likewise prevent clopidogrel's antiplatelet effects. It is not advised to use clopidogrel and CYP2C19 inhibitors (such as omeprazole and etravirine) together until further information is obtained. Furthermore, as omeprazole may cause the development of adverse drug reactions, treatment with this medication should be carefully reviewed in older patients. Indeed, we have previously reported on the delirium that developed in an older man, which was most likely caused by a drug-drug interaction (DDI) between omeprazole and amitriptyline through CYP2C19 inhibition [54]. CYP3A4 and 2C8 are involved in the metabolism of amiodarone; in vitro, amiodarone inhibits CYP3A4, 1A2, 2C9, and 2D6. Owing to its lengthy half-life (about 30 days), the risk of interaction needs to be increased during and after amiodarone treatment. Desethylamiodarone, its primary metabolite, is a competitive inhibitor of CYP2D6, an irreversible inhibitor of CYP2A6, 3A4, and 2B6 (for the formation of covalent bonds), as well as a mixed inhibitor of CYP1A1, 1A2, 2C9, and 2C19. Nevertheless, the risk of interactions may also be influenced by these metabolites [55]. Similar to this, sildenafil serum concentrations can rise up to 11 times with HIV protease inhibitors like ritonavir and saquinavir [56]. Similarly, azole antifungal medications, such as voriconazole, ketoconazole, itraconazole, and posaconazole, have been shown lately to be CYP3A inhibitors capable of inducing DDIs [57]. Posaconazole, in particular, has inhibitory effects on CYP3A and PGP. It can decrease the steady-state clearance of cyclosporine from 1.2 to 1.5 times at a dose of 200 mg for ten days. Furthermore, posaconazole (400 mg twice daily) therapy for 14 days raised the plasma concentrations of tacrolimus by 2.2 fold, the area under the curve (AUC) by 4.5 fold, and the half-life by up to 7.5 hours in an open-label research including 36 healthy participants [58]. As a result, when posaconazole is present, tacrolimus dosages should be lowered by up to 66% of their initial amounts. Given that comparable dose-related adverse events (DDI) have been reported in patients receiving either sirolimus or everolimus, an empirical 50% dosage reduction for both medications may be taken into consideration. However, Kapil et al, [59] reported that there was no clinically significant CYP3A4 interaction found between ketoconazole and transdermal buprenorphine administration in a single-center research including 20 healthy participants. It makes sense to administer a high clearance medication parenterally to avoid exposure to the gut wall and the first-pass effects on the liver of CYP3A4.

Metabolic-intermediate complexes - An uncommon type of inhibition occurs when metabolic-intermediate complexes are formed, in which the inhibitor binds exclusively to the enzyme-substrate complex. N-alkyl substituent-containing inhibitors cause the development of metabolic-intermediate complexes. Following the inhibitor's binding, 3A4 oxidises it. The resulting oxidised form of the inhibitor then stays complexed with the reduced heme group of CYP3A4, creating a slowly reversible complex. Clarythromycin has lower inhibitory effects with high clinical

effectiveness, while erythromycin, a well-known CYP3A4 inhibitor, uses this method of inhibition [60, 61].

Non-competitive - Because there is an allosteric site, the inhibitor and substrate do not fight for the same active site in the non-competitive pathway. The active site's conformation changes, its capacity to bind the substrate diminishes, and product synthesis stops once a ligand binds the allosteric site. The CYP isoforms are non-competitive inhibitors of omeprazole, lansoprazole, and cimetidine, among other medications [62, 63]. If new enzymes need to be created after the inhibitor medication is stopped, the length of this kind of inhibition can be prolonged.

Irreversible inhibition - The metabolite produced when CYP3A4 oxidises the substrate is covalently linked to 3A4 and becomes irreversible, permanently inhibiting the enzyme. The total quantity of the inhibitor that the CYP isoenzyme is exposed to, as opposed to its concentration, is the essential aspect in the case of irreversible inhibition. Drugs with large molecular sizes and lipophilicity are more likely to block [25]. A drug is sensitive to inhibitory interactions if it possesses two features: only one metabolite can account for more than 30–40% of the drug's metabolism, and only one isoenzyme can catalyse that metabolic route [48]. An inhibitor will slow down the substrate's metabolism, which will often enhance the substrate's toxicity or the drug's impact. The impact is lessened if the medication is a pro drug. In an open-label trial, Garraffo et al, examined the effects of tadalafil 10 mg pharmacokinetics on single-dose administration and steady-state concentrations of tipranavir 500 mg and ritonavir 200 mg combination [64]. The authors reported that the dose of tadalafil should be decreased at the start of antiretroviral therapy and that a full dose can be restored when steady state is established; even if the antiretroviral activity of both tipranavir and ritonavir may not be diminished. The risk of myopathy and rhabdomyolysis may rise if 3A4 inhibitors are used concurrently with hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins; simvastatin [65, 66]. It is crucial to realise, nevertheless, that myopathy may also develop for metabolic saturation while on statin medication, and especially if polytherapy is being used [67].

Metabolic induction - Although less frequent than inhibition-based medication interactions, pharmacological interactions involving enzyme induction are still quite significant and therapeutically significant. CYP enzymes can be induced by exposure to environmental contaminants and a variety of lipophilic medications. The most frequent mechanism is the synthesis of more CYP enzyme proteins as a result of transcriptional activation [61]. All that induction does is raise the concentration of P450 and expedite a drug's oxidation and elimination [43]. Rifampicin [68 - 76], phenobarbital [76, 77], phenytoin [77, 78], carbamazepine [78 - 80], and anti-tubercular medications are the most often used enzyme inducers [79]. Although CYP2A6, CYP2C, and CYP2B6 have also been seen to be weakly induced, rifampicin mostly activates CYP3A enzymes in the liver. Many medications, including quinidine, midazolam, cyclosporine A, and several steroids are substrates for CYP3A4, although rifampicin enhances their excretion. The impacted drug's metabolism increases, which reduces the strength and durability of the drug's effects [81]. Because of the half-life and the enzyme turnover, which are two parameters that affect the time-course of induction, it is relatively difficult to forecast the induction period of an enzyme. The fact that the induction time course is dependent on the amount of time needed for both enzyme breakdown and the synthesis of new enzymes complicates matters. While phenobarbital has a half-life of 3-5 days, it takes around 1 week for induction (CYP3A4, CYP1A2, CYP2C) to become obvious, rifampicin's short half-life for induction (CYP3A4, CYP2C) to become visible within 24 hours. These enzyme-induction events can shorten a medication's duration of effect by boosting its metabolic clearance. They also happen with smoking and prolonged alcohol or drug use. We recently reported a dose-dependent interaction (DDI) between phenobarbital and lamotrigine that resulted in the development of leukopenia and thrombocytopenia in an epileptic patient. We hypothesised that the haematologic effects seen may be caused by reactive metabolites of lamotrigine, which are produced as a result of phenobarbital inducing CYP enzymes [82].

DDIs during excretion - The disposal of pharmaceuticals is carried out via the kidneys, liver, lungs, faeces, perspiration, saliva, and milk, among other organs and vehicles. There is minimal quantitative relevance to the medications excreted through saliva, perspiration, and the lungs (for volatile pharmaceuticals), but the milk is crucial if the drugs can get to the infant during nursing. Drugs are excreted mainly through:

- Renal tubular excretion (glomerular filtration, tubular reabsorption and active tubular secretion)
- Biliary excretion [83].

When a medication is eliminated from the body, it may interact with other medicines in the same organ as the one it is evacuated from [84]. The organ in charge of getting rid of medicines and

their metabolites is the kidney. When two or more medications share a transport route, an interaction may arise due to a process of competition at the level of active tubular secretion. NSAIDs serve as an example of how to predict the onset of methotrexate's harmful effects when the anti-proliferative medication's renal excretion is inhibited [85]. Additionally, it was shown that amoxicillin lowered methotrexate's renal clearance [86]. Probenecid raises the area under the curve (AUC) of oseltamivir by 2.5 times. Probenecid is a strong inhibitor of the anionic route of renal tubular secretion [87]. Nonetheless, therapeutic benefits may be derived from this pharmacological competition. Probenecid, for instance, can raise the serum content of cephalosporins and penicillins, postponing renal elimination and resulting in dose savings. Probenecid really works by competitively blocking an organic anion transporter in the renal tubules, which raises the plasma concentrations of other substrates of transporters while decreasing their excretion [88]. Numerous medications have the ability to obstruct tubular transit. Specifically, the H_2 receptor inhibitor cimetidine may affect the secretion of several chemicals from tubules. Despite normal renal function, it may alter the serum concentration of other drugs due to its impact on the inflow and efflux of organic cations through the human organic cation transporters (hOCT1 and hOCT2) and the human multidrug and toxin extrusion (hMATE1 and hMATE2-K) [89]. Furthermore, an in vitro investigation revealed that PPIs, such as omeprazole, pantoprazole, lansoprazole, rabeprazole, and tenatoprazole, are strong inhibitors of hOCT and may affect the way metformin is transported [90]. But it might be clearer how useful these DDIs are clinically. Interactions may also arise during the process of tubular reabsorption. When present in the urine in an ionised state, many medicines diffuse across tubular cells. Pharmacologically induced variations in urine pH can impact the degree of ionisation of specific medications and consequently have an impact on the drug's reabsorption from the renal tubule [91]. Specifically, absorption of acidic medications is decreased in urine with an alkaline pH, whereas absorption of basic pharmaceuticals is decreased in urine with an acidic pH. However, variations in urine pH only become practically significant if the drug's pKa, or the pH at which half of the molecules in solution are ionised, falls between 3.0 and 7.5 for acids and between 7.5 and 10.5 for bases. As a matter of fact, the pKa values have the ability to significantly alter the drug's degree of dissociation. Because they may alter the pH of urine, compounds like tromethamine, ammonium chloride, and diuretics can influence the excretion of both basic and acidic medications [15]. This interaction can be utilised to help the body eliminate pharmaceuticals. Conversely, the patient may nonetheless have adverse consequences from the combination of diuretics and lithium salts. Changes in serum sodium levels have an impact on the excretion of lithium, a monovalent cation. Consequently, a high sodium excretion brought on by long-term use of certain diuretics, such thiazides, may enhance the reabsorption of lithium, potentially leading to dangerous toxic side effects from relative overdosage [92, 93]. Active transport is used to move some highly ionised acidic and basic medications across the renal tubule epithelium. The availability of the transporter, a protein that permits the transfer across cellular membranes, determines how quickly molecules may move across them. Consequently, two medicines that are substrates of the same transmembrane transporter can complement one another up to the point at which the transporter's capacity is saturated. At that point, the rate of elimination becomes closer to a process that is zero order, or saturable.

Strategies to prevent pharmacokinetic DDI

For medical professionals, the Summary of Product Characteristics (SPCs) is the main source of information on DDIs. Regretfully, DDI is too many to mention them all. Because of the restricted space in the SPC, the information on possible DDIs may not be fully stated. According to the risk described in the Italian SPCs of PPIs, it was discovered in a cross-sectional study conducted in Italy that 3.0% of PPI users were potentially exposed to DDI within a year of follow-up. However, this proportion increased to 9.0% when information about the DDI risk associated with PPIs was taken into account, as reported by Drugdex [94]. As a result, studies on DDI that take into account many sources and are updated based on the most recent data from the literature ought to be helpful in assessing the potential risk of DDI, especially in older patients receiving polytherapy. Furthermore, even though they aren't always practical or available, the implementation of therapeutic drug monitoring protocols in the elderly patients with comorbidities treated with multiple drugs mentioned above should be seen as a crucial tool to reduce the frequency and severity of DDIs that could result in higher health system costs or legal liability for the treating physicians. As a result, we expect that the National Health System would develop an intervention strategy to ensure that doctors are appropriately informed about potential DDI, especially with reference to commonly used drugs. But at this point, studies on DDIs that take into account many sources and are updated based on recent findings from the literature

could be helpful in assessing a potential risk of DDI, especially in older patients receiving polytherapy. It has previously been documented that CYP enzyme genetic polymorphism significantly contributed to the formation of DDIs as well as the clinical outcomes of medication treatment [7, 95 - 97]. Therefore, even though they aren't always practical or available, adopting therapeutic drug monitoring in patients receiving multiple drug treatments as well as using in vitro methods to determine how CYP enzyme polymorphism contributes to DDIs should be viewed as crucial tools to reduce the frequency and severity of DDIs.

III. Discussion and Conclusion

Managing patients who are receiving several pharmacological treatments, DDIs are a typical clinical issue. It should be noted, nonetheless, that just two medications have the capacity to cause DDIs, even if the pharmacology of each medication plays a role in its clinical significance. Indeed, in the presence of medications with a long half-life, a low therapeutic index, and a stronger binding with plasma proteins, a DDI will be able to provide a clinically meaningful impact. Furthermore, it is critical to emphasise that the development of DDI is an issue specific to a particular medicine rather than a class of drugs, and that this concern may be underestimated when looking simply at the SPC.

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