

Review

## Drug Interactions Pharmacology: A Narrative Review

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### Article history

Received: 01-06-2022

Revised: 14-09-2022

Accepted: 03-10-2022

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**Abstract:** The simultaneous prescription of multiple drugs used in therapeutic schemes can result in drug interactions, with desirable or undesirable effects. Thus, the objective of this study was to describe the mechanisms involved in clinically relevant drug interactions. This is a narrative review in which studies published in PUBMED and the VHL were searched in the following databases: MedLine, Lilacs, and Scielo. The search was performed in May 2021, after reading the articles and their references. The results showed that drug interactions occur through the co-administration of different compounds. In this context, drugs can suffer pharmaceutical interactions due to different physical-chemical processes, as well as after administration, interfering in the mechanisms of absorption, distribution, metabolism, and elimination of pharmacokinetics or pharmacodynamics, with changes in the pharmacological effect. Such mechanisms can cause undesirable outcomes, such as increased toxicity or impairment of therapeutic effect, or be used as a strategy for beneficial interactions to increase the pharmacological effect or reduce toxicity. Given the clinical impacts that may occur due to drug interactions, knowledge about the different mechanisms involved in drug interactions is essential.

**Keywords:** Drug Interactions, Polypharmacy, Pharmacology, Clinical Pharmacology

## Introduction

Over time, special attention has been paid to problems related to drug prescribing, since adverse events are frequently observed and are a potential source of harm to patients, constituting a public health problem (Neto *et al.*, 2017). This is explained by the common concurrent prescription of multiple drugs used in therapeutic regimens, to improve drug efficacy, reduce toxicity and treat co-existing diseases (Secoli, 2001).

Thus, polypharmacy can result in Drug Interactions (DI), which, according to the Food and Drugs Administration, occur when two or more drugs react with each other and can reduce or increase the effectiveness of a particular drug or cause unexpected side effects. With this, one does not have the clinical and pharmacological effects of the drug when administered alone, so there is the possibility of having additive (synergistic), antagonistic, or unexpected responses (Hermann *et al.*, 2018).

It is important to note that, besides polypharmacy, other factors can culminate in the occurrence of DI, which are related to the intrinsic conditions of the patient, such as age, sex, diet, the nature and number of diagnosed diseases; and intrinsic factors to the drug, such as its pharmacokinetics and pharmacodynamics (Leao *et al.*, 2014). So, the complexity of a prescription rises in the presence of one or more risk factors for DI (Leao *et al.*, 2014).

Although there are studies in the literature that estimate the prevalence and severity of DI, those focused on the mechanisms involved in these interactions are scarce. Therefore, the development of studies directed to this theme is essential to allow the knowledge of ways to reduce the risk of adverse effects of DI in a world with increasing drug use.

Given these premises, the objective of the present study was to describe the mechanisms involved in clinically relevant DI through a narrative review of the literature indexed in scientific databases on the topic.

## Materials and Methods

This is a narrative review of studies published in PUBMED and in the Virtual Health Library (VHL-Bireme), by databases: Medical Literature Analysis and Retrieval System Online (MedLine), Latin American and Caribbean Literature on Health Sciences (Lilacs), and portal of the Scientific Electronic Library Online (SciELO). The search was conducted in May 2021, from the reading of the articles, guided by the following question: Which mechanisms are involved in drug interactions?

Published studies that met the following inclusion criteria were selected for this review: Full-text availability in Portuguese and/or English, systematic review or meta-analysis of all randomized controlled trials, non-randomized controlled trials, case-control studies, and published cohort studies in which the topic involved the mechanisms intrinsic to DI. The exclusion criteria adopted were opinion studies by authorities, expert committee reports, editorials, dissertations, monographs, and theses. The references of the selected articles were analyzed to identify other articles that met the previously established criteria and that were not located in the consulted databases.

In the initial research, the identification phase, the articles were searched in the selected databases. In the next step, the selection was made by reading the titles and abstracts of the articles. After reading these articles in full and verifying the focal theme of the research, the articles that did not meet the inclusion and exclusion criteria were excluded. The references were analyzed and the studies that fit the inclusion and exclusion criteria were selected.

To access the full text, the following resources were used: Link available directly from the selected database, search on the portal of the journal in which the article was published, and search on the Capes portal.

Given the secondary nature of the data, the Ethics and Research Committee was waived according to the norms previously established in Brazilian ethics committees.

## Results and Discussion

Drug interactions due to the co-administration of different compounds can occur at different stages of the process to which the drug is submitted (Li *et al.*, 2019). Thus, drugs can undergo physical-chemical interaction before administration and absorption or in the processes of the different pharmacological phases: Pharmacokinetics, with potential interference in absorption, distribution, metabolism, and elimination, or pharmacodynamics, with changes in the pharmacological effect (Li *et al.*, 2019; Niu *et al.*, 2019; Secoli, 2001). These different mechanisms of interactions can generate negative results, with increased toxicity or hindrance of the therapeutic effect, as well as can be used as a strategy for beneficial interactions, with the potential to increase

the pharmacological effect and reduce toxicity (Queiroz *et al.*, 2014).

### *Pharmaceutical Interaction*

Pharmaceutical interactions result from contact between two or more active ingredients and/or adjuvant components of the formulation. They can result in the decrease or inactivation of the pharmacological effect, alter the toxicity or form a new active compound (Marsilio *et al.*, 2016). The interactions can occur due to different chemical and physical processes, by different decomposition reactions, such as hydrolysis, oxidation, and photolysis, or by adsorption, precipitation, and chelation (Leal *et al.*, 2016; Paes *et al.*, 2017).

Adsorption is a binding reaction with substances, which prevents the absorption of a drug. One beneficial interaction by adsorption reaction is the use of activated carbon to prevent the absorption of drugs in cases of poisoning, thereby decreasing the bioavailability and toxic effects of the drug (Chiew *et al.*, 2018). For its use to be effective it must be administered in intoxications by substances that can bind to carbon, in this group are included several drugs, such as paracetamol, barbiturates, anti-epileptics, and antihistamines (Chiew *et al.*, 2018; Zellner *et al.*, 2019).

The chelation reaction turns a soluble and absorbable drug into an insoluble and non-absorbable one. This mechanism can occur during the co-administration of magnesium/aluminum-containing antacids and different drugs, such as ciprofloxacin. Another example is the ingestion of orange juice concomitant with fluoroquinolones. The interaction between the cation and the drug forms an insoluble chelating complex with low absorption, which leads to reduced bioavailability of the drug (Chen *et al.*, 2018; Patel *et al.*, 2020).

### *Pharmacokinetic Interaction*

The joint administration of drugs, herbal medicines and food is capable of altering the pharmacological bioavailability, due to alterations in the stages of pharmacokinetics (Akbulut and Urun, 2020; Niu *et al.*, 2019). Interactions of this type are important for clinical practice, particularly in drugs with a narrow therapeutic window, where the limit between therapeutic and toxic doses is lower (Secoli, 2001).

### *Interactions During Absorption*

Gastrointestinal motility, pH, and content are under the constant influence of the prandial state of the individual. Enterally (orally) administered drugs, absorbed in the lumen of the Gastrointestinal tract (GI tract), are directly impacted by changes in this environment, which may or may not favor bioavailability (Secoli, 2001).

The degradation of the pharmaceutical form makes the active ingredient available in the GIT lumen, where it will be dissolved to be absorbed. The degree of ionization of the molecules, the result of the interaction between the pH of the medium and the ionization constant (pKa) of the drug, is crucial in this step because non-ionized molecules have greater lipophilicity and ease of being passively absorbed by cell (Becker and Reed, 2012). The alkalization of gastric pH by omeprazole, for example, reduces the oral bioavailability of ketoconazole and itraconazole; weak bases that need the acidic pH of the stomach to take on the non-ionized form (Wedemeyer and Blume, 2014).

Some drugs are unstable in acidic media-penicillin G, erythromycin, and digoxin-in which variations in stomach pH influence the rate of degradation and bioavailability, being favored by the elevation of stomach pH after pretreatment with omeprazole, for example (Abuhelwa *et al.*, 2017). Didanosine, an antiretroviral drug, also suffers this same effect and, therefore, combined formulations with antacids are marketed, to confer greater stomach stability to the drug (Severino *et al.*, 2014).

Binding between drugs and divalent metal ions present in food can also alter pharmacological availability, due to the formation of insoluble, inactive complexes. Administration of norfloxacin with milk or yogurt is sufficient to reduce its bioavailability by 50%, as do tetracyclines (Abuhelwa *et al.*, 2017). Cholestyramine and colestipol, on the other hand, bile acid scavengers, can form complexes with antidepressants, digitalis, and anticoagulants, which reduces absorption (Riaz and John, 2021).

Sucralfate, for example, forms a barrier to the mucosa of the gastrointestinal tract, protecting it against ulcers. Thus, it acts as a bioavailability reducer of fluoroquinolones by forming stable chelation complexes between the aluminum in its molecule and the fluoroquinolones, which reduces absorption (Sulochana *et al.*, 2016).

The rate of gastric emptying and intestinal motility define the speed and degree of absorption of drugs, which is why drugs that act on the motility of the gastrointestinal tract when in joint therapy, can influence the bioavailability of other compounds (Corrie and Hardman, 2011).

Metoclopramide is a prokinetic that stimulates serotonin 5-HT<sub>4</sub> receptors, antagonizes presynaptic inhibition of muscarinic receptors, and blocks dopamine D<sub>2</sub> receptors. Thus, the release of acetylcholine induces increased intra-gastric pressure, which is responsible for accelerating emptying. When co-administered, it tends to increase the absorption of other compounds, because it exposes them more rapidly to the extensive intestinal absorptive area (Shakhatreh *et al.*, 2019).

Erythromycin and azithromycin are antimicrobials that act on motilin receptors and increase the contraction of the stomach antrum, so they are used off-label for

diabetic gastroparesis (Shakhatreh *et al.*, 2019). Dopaminergic antagonists and laxatives, except castor oil, increase the risk of toxicity of other agents by increasing absorption and reducing the time to maximum serum concentration (Boyce *et al.*, 2012; dos Santos *et al.*, 2018).

Opioids, such as morphine, reduce intestinal motility due to their action on opioid receptors in the myenteric plexus, while anticholinergics, such as atropine, delay gastric emptying and decrease gastrointestinal motility by blocking muscarinic receptors. Both of these effects tend to reduce the absorption of concomitant drugs (Feng *et al.*, 2017; Secoli, 2001).

The passage of the drug through the intestinal mucosa is an essential step for bioavailability and efficacy at the target site. However, this mucosa is a highly specialized surface composed of microvilli and transmembrane transport proteins expressed on the basolateral and apical membranes of enterocytes that mediate the capture and efflux of compounds from the intestinal lumen (Müller *et al.*, 2017).

Ten to twenty different proteins have been characterized for mediating oral drug absorption in humans, however, the ABC family transporters-glycoprotein P (Gp-P), Multidrug Resistance-associated Protein type 2 (MRP2), and Breast Cancer Resistance Protein (BCRP) -are the most studied. However, the expression pattern of these transporters differs from person to person and may also be regulated by the presence of underlying diseases, such as inflammatory disorders and cancer (Mollazadeh *et al.*, 2018; Müller *et al.*, 2017).

Some drugs such as rifampin and carbamazepine are activators of nuclear receptors responsible for regulating the expression of transport proteins present in enterocytes. This effect can result in drug interactions by accelerating the transport pathways of the co-administered drugs (Müller *et al.*, 2017).

Gp-P functions as an efflux pump, transporting xenobiotics out of hepatocytes and enterocytes. It interferes with the absorption of drugs that may induce, inhibit, or compete for its binding site. This glycoprotein is also present at the blood-brain barrier and, when overexpressed, may cause resistance to anticonvulsant treatment by rapidly removing them from the central nervous system (Bishop, 2018; Mollazadeh *et al.*, 2018).

Verapamil, a Gp-P inhibitor, when co-administered with digoxin, increases the plasma concentration of this digitalis. Loperamide, a substrate of Gp-P, when co-administered with Gp-P inhibitors, can cross the blood-brain barrier and cause central opioid effects such as respiratory depression. Hypericum perforatum, on the other hand, is an inducer of Gp-P and, therefore, induces the expulsion of drugs such as cyclosporine, an immunosuppressant used in transplants, whose interaction can result in rejection of the transplanted organ (Cascorbi, 2012; Posadzki *et al.*, 2013; Regnard *et al.*, 2011).

Facilitated transport systems, although saturable, also mediate drug absorption. Levodopa, for example, competes with dietary amino acids for facilitated transport and therefore has reduced therapeutic efficacy in patients with high protein intake (Cooper *et al.*, 2008).

Organic Anion Transporter Polypeptides (OATPs), a superfamily of carrier proteins, promote the influx of their substrates into the intestine. OATPs interfere with the absorption of drugs susceptible to modulation of action. Administration of green tea, an OATP inhibitor, concomitantly with atenolol, a substrate of the OATPs, results in reduced efficacy of the beta-blocker by impairing absorption (Yu *et al.*, 2017).

The viscosity of mucus within the GIT lumen is another factor that alters drug absorption. When increased in the postprandial period, it can serve as a physical barrier to the passage of substances through the mucosa. Thus, the bioavailability of budesonide is significantly reduced when co-administered with solid meals. On the other hand, drugs that impair the integrity of the gastrointestinal epithelium, such as colchicine, cause blockage of local active transport, which impairs the absorption of other agents (Abuhelwa *et al.*, 2017; Davis *et al.*, 2013).

The gut microbiota, composed of trillions of bacteria that colonize the human GIT, has a major influence on metabolic processes at the local and systemic levels. It thus affects how an individual responds to a drug by influencing the bioavailability, bioactivity, and toxicity of exogenous agents (Weersma *et al.*, 2020).

Similarly, xenobiotics and pathological states of inflammatory, metabolic, neurological, or autoimmune nature may be associated with intestinal dysbiosis, which also affects the ability to metabolize and absorb orally administered drugs (Weiss, 2017; Zhang *et al.*, 2019).

Broad-spectrum antibiotics, for example, due to their antibacterial activity have an intrinsic potential to cause both transient and long-term dysbiosis, which can potentiate the effect of oral anticoagulants, due to reduced vitamin K synthesis and increase the absorption of digoxin by suppressing gastrointestinal biotransformation (Louvison *et al.*, 2008; Yan *et al.*, 2018).

The entero-hepatic circulation can also influence the pharmacological bioavailability, because, through it, the xenobiotics are brought from the liver to the small intestine by the bile, where they can be reabsorbed back to the liver. Ethinyl estradiol, which makes up combined oral contraceptives, after extensive first-pass metabolism, must undergo enterohepatic circulation for a breakdown of the metabolite conjugates and re-entry into the bloodstream (Malik *et al.*, 2016).

However, broad-spectrum antibiotics such as ampicillin, amoxicillin, azithromycin, and quinolones, by suppressing the intestinal microbiota, eliminate the bacteria responsible for producing glyburonidases, enzymes that cleave the conjugates of oral contraceptives. This can result in contraceptive failure, bleeding, and unwanted pregnancy (Elomaa *et al.*, 2001).

### *Interactions During Distribution*

After being absorbed, the drug needs to be distributed through systemic circulation to the intra- and extracellular compartments until it reaches its target organ. However, factors such as the drug's affinity for tissues, blood flow, and binding to plasma proteins can interfere with distribution (Currie, 2018; Franco *et al.*, 2007).

Plasma proteins, mainly albumin, function as a pharmacological transport and reservoir. Drug-drug interactions that alter the degree of albumin binding are clinically relevant due to the increased pharmacological and toxic effects of displaced drugs, especially those that have a low therapeutic index (Benet and Hoener, 2002; Tesseromatis and Alevizou, 2008).

Drugs can be displaced from albumin in a direct way when active principles or metabolites compete for the same albumin binding site. Thus, drugs with higher affinity for proteins and administered in high concentrations, occupy protein binding sites and displace compounds with lower affinity, transiently increasing they're on and off-concentration (Tayyab and Feroz, 2021; Tesseromatis and Alevizou, 2008).

Warfarin is extensively bound to plasma albumins. Therefore, concomitant administration of a drug that also binds to the same plasma albumin binding site, such as fluoxetine, NSAIDs, or acid antibiotics ( $\beta$ -lactams), decreases its protein-binding capacity and increases the amount of free drug, potentiating its anticoagulant effect (Teles *et al.*, 2012; Tesseromatis and Alevizou, 2008).

Another type of interaction, called non-competitive displacement, happens when a drug, when interacting with albumin, promotes changes in the tertiary structure of the protein. This interferes with the affinity for specific pharmacological groups. AAS presents a peculiar pattern of interaction with albumin since it can acetylate lysine residues of the molecule (Kragh-Hansen *et al.*, 2002; Yamasaki *et al.*, 2013).

### *Interactions During Metabolism*

Pharmacological metabolism is divided into two phases: Phase I, in which polar groups are formed or added to the molecule by oxidation reactions or hydrolysis; and phase II, in which the molecule is conjugated with hydrophilic groups such as glyburonic acid. Thus, the compounds may be transformed into active, inactive, or water-soluble molecules (El-Sherbeni and El-Kadi, 2017; Guimarães and Godoy, 2008).

Cytochrome P450 (CYP) is a superfamily of enzymes ubiquitous in almost all human tissues. In the liver, they are the main catalysts of phase I reactions and in the intestine, they are the first site of biotransformation of oral drugs via first-pass metabolism (Alqhtani *et al.*, 2018; El-Sherbeni and El-Kadi, 2017).

Therefore, drugs that have extensive first-pass metabolisms, such as propranolol, metoprolol, and albendazole, have their bioavailability favored by the ingestion of fatty foods, due to the detour of the compound to the lymphatic system along with the chylomicrons (Đaković-Švajcer, 2002).

Because of the wide range of drugs they metabolize, any factor or agent that affects the expression and/or activity of CYPs can significantly change biotransformation, especially in patients with hepatic or renal failure. The induction of CYPs happens through gene transcription activated by xenobiotics after they are bound to receptors and internalized in the cell nucleus. Therefore, it is a long process and its main inducers are anticonvulsants, rifampicin, corticoids, cigarettes, and chronic alcohol consumption (Krau, 2013; Manikandan and Nagini, 2018; Nunes *et al.*, 2017; Secoli, 2001).

For most drugs, induction of CYPs causes increased metabolization and suppression of the therapeutic effect, however, for pro-drugs, this results in increased production of active metabolites. Rifampicin, for example, is an inducer of CYP2C and CYP3A, which reduces the therapeutic efficacy of concomitantly used oral contraceptives (Baciewicz *et al.*, 2013; Krau, 2013).

CYP3A4 induction by St. John's wort (*Hypericum perforatum*), when administered with cyclosporine, reduces the immunosuppressant plasma levels, increasing the risk of transplant organ rejection. The induction of CYP2B6 by phenytoin or phenobarbital alters the pharmacokinetics of cyclophosphamide, by increasing its metabolism. Some drugs can also induce their metabolism (auto-induction), which happens with potent inducers of CYP3A4 such as phenytoin and rifampin (Braz *et al.*, 2018; Manikandan and Nagini, 2018).

Inhibition of CYPs, the main drug interaction mechanism in biotransformation, causes an increased risk of toxicity or reduces the therapeutic effect of prodrugs and can occur reversibly or irreversibly. Reversible inhibition lasts according to the half-life of the inhibitor and can be competitive, noncompetitive, and uncompetitive (El-Sherbeni and El-Kadi, 2017; Manikandan and Nagini, 2018).

Competitive inhibition occurs when two agents compete for the same enzyme active site, as with fluoxetine, a CYP2D6 inhibitor, when administered with metoprolol. In the noncompetitive process, the inhibitor binds to the allosteric site and regulates enzyme activity, as tamsulosin does with CYP3A1/2 and in the uncompetitive process, the inhibitor binds to the enzyme-substrate complex, as cotidine does with CYP2E1 (Cascorbi, 2012; El-Sherbeni and El-Kadi, 2017; Manikandan and Nagini, 2018).

Irreversible inhibition is caused by substrates that first have to be transformed by CYP into active metabolites, the inhibitor-suicides. These agents form highly stable

covalent bonds with the enzyme and thus produce inactivation (El-Sherbeni and El-Kadi, 2017; Manikandan and Nagini, 2018).

Tamoxifen, for example, used to treat breast cancer, is known to be a potent inhibitor-suicide of CYP2B6, CYP2D6, and CYP2C9. On the other hand, the furocoumarins in grapefruit juice can inactivate exclusively intestinal CYP3A, which impairs the absorption of orally administered drugs such as cyclosporine (Hanley *et al.*, 2011; Manikandan and Nagini, 2018).

In addition, the administration of statins such as simvastatin and atorvastatin with CYP inhibitors-ketoconazole and erythromycin, for example-causes increased bioavailability and risk of adverse effects such as myotoxicity and rhabdomyolysis. Pro-drugs such as codeine and tramadol, which are metabolized by CYP2D6, have a lower formation of active metabolites when administered with inhibitors such as paroxetine (Braz *et al.*, 2018; Krau, 2013).

Fluconazole, a potent CYP2C9 inhibitor, should be administered with caution together with warfarin because due to the inhibition of metabolism of the anticoagulant there is an increased risk of bleeding. CYP2C19, inhibited by omeprazole, reduces the activation of clopidogrel when co-administered since this antiplatelet is a pro-drug (Braz *et al.*, 2018).

Phase II reactions, mainly glyburonidation, are also the target of drug interactions due to the modulation of enzyme action by drugs or physiological status. In neonates, for example, hepatic immaturity renders phase II metabolization inefficient, due to a lack of UDP-glycuronyltransferase. Thus, administration of chloramphenicol can cause accumulation of this compound in tissues in the infant, a condition known as gray baby syndrome (Gato *et al.*, 2018; Oong and Tadi, 2021).

Another factor interfering with drug metabolism is hepatic blood flow. Drugs extensively metabolized by the liver, such as lidocaine, undergo an increase or decrease in half-life when administered with propranolol and isoprenaline, respectively (Corrie and Hardman, 2011).

### *Interactions that Modify Excretion*

Excretion consists of the final elimination of compounds in unchanged form or bio-transformed to metabolites with greater polarity. This process can occur through different routes, such as sweat, tears, breast milk, bile, saliva, urine, or in gaseous form through the lungs. Among these routes, renal excretion stands out as the main responsible for the elimination of most drugs and metabolites. The elimination of compounds by the kidneys may suffer interference from urinary pH or renal blood flow (Garza *et al.*, 2021). However, changes in the permeability of glomerular filtration or the transporters of tubular secretion and reabsorption are even more important, because they can modify the amount of the

compound eliminated or reabsorbed (Currie, 2018; Yin and Wang, 2016)

Gp-P, for example, acts in the transport of different drugs, among them analgesics, chemotherapeutics, antihistamines, and calcium channel blockers. Gp-P has been identified at different sites, such as the Blood-Brain Barrier (BBB), hepatocytes, intestinal columnar epithelial cells, and the kidneys. The expression of Gp-P in the apical membrane of proximal tubule cells corroborates its important role in renal excretion. In vivo studies reveal that the co-administration of Gp-P inhibitors, such as verapamil, increases the half-life, bioavailability, and toxicity of digoxin by reducing renal secretion (Hee Choi and Yu, 2014; Ledwitch and Roberts, 2017; Yin and Wang, 2016).

Most renal drug interactions are undesirable; however, some co-administrations can be used beneficially. Probenecid, for example, was developed to act as an inhibitor of the secretion of renal organic anions. This mechanism decreases the clearance of penicillin and consequently increases the systemic concentration of the drug (Li *et al.*, 2019).

Another important factor that can directly impact excretion is urinary pH since drug ionization can vary according to the pH range of the urine. In this context, acidic drugs have increased excretion in basic urine and the same is true for basic drugs in acidic urine (Garza *et al.*, 2021). This characteristic can be used as an antidote strategy in cases of phenobarbital intoxication, for example, in which sodium bicarbonate is administered to alkalize the urine and increase the elimination of phenobarbital (Murty, 2019).

### *Pharmacodynamic Interaction*

Pharmacodynamic interactions happen when the effects of a drug are modified by the interference of another compound at its site of action or through physiological mechanisms. It can happen through six different mechanisms: Addition, addition, potentiation, synergism, antagonism, and receptor modulation (Brasil, 2012; Feng *et al.*, 2017).

Addition occurs with drugs with the same mechanism of action that, when administered together, produce therapeutic and toxic effects corresponding to the sum of the effects in isolated administration. In addition, the addition occurs when drugs in joint use produce the therapeutic effect corresponding to the sum of the individual effects; however, it occurs between drugs that have different mechanisms of action and without increasing the adverse effects. An example of this is the association between fenoterol (muscarinic receptor inhibitor) and ipratropium bromide (beta2-adrenergic agonist) for the treatment of asthma. There is also the joint use of the beta blocker atenolol with amlodipine, a calcium channel inhibitor, in hypertension and chronic

stable angina (Tale *et al.*, 2019; Wongwaree and Daengsuwan, 2019).

Potentiation, on the other hand, consists of the use of an inactive drug together with an active one. Thus, the inactive compound becomes the target of biological mechanisms capable of inactivating the active drug, which enables greater bioavailability. In the treatment of Parkinson's disease, the combination of levodopa and carbidopa is an example of potentiation, since carbidopa, being a dopa-decarboxylase inhibitor, protects levodopa from its action. The same happens with amoxicillin and clavulanic acid, which inhibits the beta-lactamase capable of inactivating amoxicillin (Hayes *et al.*, 2019; Huttner *et al.*, 2020).

In synergism the effect of the interaction is greater than the sum of the effects of the individual drugs, considering that they have different mechanisms of action. The combination between trimethoprim and sulfamethoxazole is an example of synergism widely used in the treatment of infections by Methicillin-Resistant Staphylococcus Aureus (MRSA). There is also a synergistic effect in the concomitant use of benzodiazepines and alcohol because both act by stimulating gabaergic inhibitory receptors in the central nervous system (Fraser *et al.*, 2012; Liang and Olsen, 2014).

Pharmacodynamic interactions can also be antagonistic and are divided into four categories: Pharmacological, physiological, chemical, and dispositional antagonism. Pharmacological antagonists cause a reduced effect due to the blockade of the receptor site of one of the administered drugs. The physiological or functional antagonists, on the other hand, interact with different receptors but have opposite actions for the same physiological function (Delucia, 2014).

In chemical antagonism or inactivation, the co-administered compounds react chemically, which causes a decrease in concentration. Dispositional antagonism implies a change in the availability of a drug due to a smaller amount of drug reaching the site of action or a shorter time of action in the body (Delucia, 2014).

The antagonism happens, for example, in the administration of anticoagulants together with vitamin K, since there is opposition to anticoagulation. Another example is the joint administration of anti-diabetics and glucocorticoids, because these predispose to hyperglycemia, impairing the treatment of diabetes (Di Minno *et al.*, 2017; Kwon *et al.*, 2013).

### **Conclusion**

Drug interactions occur due to the co-administration of different compounds, through changes in the pharmaceutical formula or the pharmacokinetic and pharmacodynamic steps. They result in undesirable effects, such as increased toxicity or impairment of therapeutic effect, but can be used as a beneficial strategy to increase the pharmacological effect or reduce toxicity.

Finally, given the different clinical impacts of drug interactions related to the increasingly frequent administration of multiple drugs, knowledge about the different mechanisms involved in drug interactions is essential to facilitate the identification and clinical management. For this, it is necessary to develop more studies involving this theme, which is still scarce in the literature.

## Acknowledgment

Thanks to the Federal University of Alagoas (UFAL), National Council for Scientific and Technological Development (CNPq), Medical Sciences and Nursing Complex (CCME), Laboratory of Biochemistry, Pharmacology, and Physiology, and the research group Morphology and Health.

## Author's Contributions

**Livia Maria Barbosa Neves, Louryanne de Castro Silva, Mônica Thalia Brito de Melo and Yasmin Vitória Silva Nobre:** Planned and executed the literature research, data analysis, organization and writing of the manuscript.

**Emanuel Tenório Paulino, Êurica Adélia Nogueira Ribeiro, Célio Fernando de Sousa Rodrigues and Amanda Karine Barros Ferreira Rodrigues:** Designed the research plan, organized and revised writing of the manuscript. All authors read and approve the final manuscript.

## Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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