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A COMPREHENSIVE REVIEW OF VARIOUS DRUG INTERACTIONS

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ABSTRACT

A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug. Drug interactions can have desired, reduced or unwanted effects. The probability of interactions increases with the number of drugs taken. The high rate of prescribed drugs in elderly patients (65-year-old patients take an average of 5 drugs) increases the likelihood of drug interactions and thus the risk that drugs themselves can be the cause of hospitalization. Drug interactions occur on pharmacodynamic and pharmacokinetic levels. Examples of pharmacodynamic interactions are simultaneous administration of a NSAID and phenprocoumon (additive interaction), or of aspirin and ibuprofen (antagonistic interaction). Pharmacokinetic interactions occur at the levels of absorption (e.g., levothyroxine and neutralizing antacids), elimination (e.g., digoxin and macrolides), and metabolism, as in the competition for cytochrome P450 enzymes (e.g., SSRIs and certain beta-blockers).

KEYWORDS: Drug interactions occur on pharmacodynamic and pharmacokinetic levels.

INTRODUCTION

A drug interaction is a change in the action or side effects of a drug caused by concomitant administration[1] with a food, beverage, supplement, or another drug. A cause of a drug interaction involves one drug which alters the pharmacokinetics of another medical drug. Alternatively, drug interactions result from competition for a single receptor or signalling pathway. Both synergy and antagonism occur during different phases of the interaction between a drug, and an organism. For example, when synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed agonists. On the other hand, in the case of antagonism, the substances involved are known as inverse agonists. The risk of a drug-drug interaction increases with the number of drugs used. Over a third (36%) of the elderly in the U.S. regularly use five or more medications or supplements, and 15% are at risk of a significant drug-drug interaction.

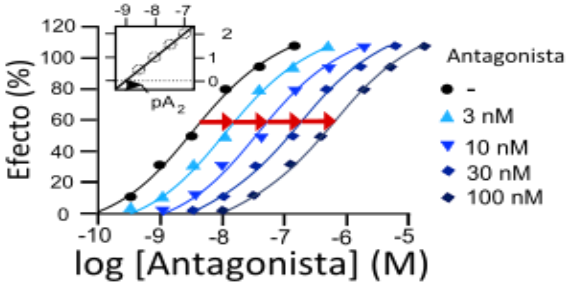
Pharmacodynamic Interactions[2]

When two drugs are used together, their effects can be additive (the result is what you expect when you add together the effect of each drug taken independently), synergistic (combining the drugs leads to a larger effect than expected), or antagonistic (combining the drugs leads to a smaller effect than expected). There is sometimes confusion on whether drugs are synergistic or additive, since the individual effects of each drug may vary from patient to patient. A synergistic interaction may be beneficial for patients, but may also increase the risk of overdose. Both synergy and antagonism can occur during different phases of the interaction between a drug, and an organism. The different responses of a receptor to the action of a drug have resulted in a number of classifications, such as "partial agonist", "competitive agonist" etc. These concepts have fundamental applications in the pharmacodynamics of these interactions. The proliferation of existing classifications at this level, along with the fact that the exact reaction mechanisms for many drugs are not well-understood means that it is almost impossible to offer a clear classification for these concepts. It is even possible that many authors would misapply any given classification. Direct interactions between drugs are also possible and may occur when two drugs are mixed prior to intravenous injection. For example, mixing thiopentone and suxamethonium in the same syringe can lead to the precipitation of thiopentone.

Pharmacodynamic interactions can occur on Pharmacological receptors: Receptor interactions are the most easily defined, but they are also the most common. From a pharmacodynamic perspective, two drugs can be considered to be Homodynamic, if they act on the same receptor. They, in turn can be Pure agonists, if they bind to the main locus of the receptor, causing a similar effect

to that of the main drug. Partial agonists if, on binding to one of the receptor's secondary sites, they have the same effect as the main drug, but with a lower intensity. Antagonists, if they bind directly to the receptor's main locus but their effect is opposite to that of the main drug. These include, Competitive antagonists, if they compete with the main drug to bind with the receptor. The amount of antagonist or main drug that binds with the receptor will depend on the concentrations of each one in the plasma.

Uncompetitive antagonists, when the antagonist binds to the receptor irreversibly and is not released until the receptor is saturated. In principle the quantity of antagonist and agonist that binds to the receptor will depend on their concentrations. However, the presence of the antagonist will cause the main drug to be released from the receptor regardless of the main drug's concentration, therefore all the receptors will eventually become occupied by the antagonist.



Effects of the competitive inhibition of an agonist by increases in the concentration of an antagonist. A drug potency can be affected (the response curve shifted to the right) by the presence of an antagonistic interaction.pA_2 known as the Schild representation, a mathematical model of the agonist: antagonist relationship or vice versa. NB: the x-axis is incorrectly labelled and should reflect the agonist concentration, not antagonist concentration.

1. Heterodynamic competitors, if they act on distinct receptors.

Signal transduction mechanisms: these are molecular processes that commence after the interaction of the drug with the receptor. For example, it is known that hypoglycaemia (low blood glucose) in an organism produces a release of catecholamine's, which trigger compensation mechanisms thereby increasing blood glucose levels. The release of catecholamine's also triggers a series of symptoms, which allows the organism to recognise what is happening and which act as a stimulant for preventative action (eating sugars). Should a patient be taking a drug such as insulin, which reduces glycaemia, and also be taking another drug such as certain beta-blockers for heart disease, then the beta-blockers will act to block the adrenaline receptors. This will block the reaction triggered by the catecholamine's should a hypoglycaemic episode occur. Therefore, the body will not adopt corrective mechanisms and there will be an increased risk of a serious reaction resulting from the ingestion of both drugs at the same time.

Antagonic physiological systems: Imagine a drug A that acts on a certain organ. This effect will increase with increasing concentrations of physiological substance S in the organism. Now imagine a drug B that acts on another organ, which increases the amount of substance S. If both drugs are taken simultaneously it is possible that drug A could cause an adverse reaction in the organism as its effect will be indirectly increased by the action of drug B. An actual example of this interaction is found in the concomitant use of digoxin and furosemide. The former acts on cardiac fibres and its effect is increased if there are low levels of potassium (K) in blood plasma. Furosemide is a diuretic that lowers arterial tension but favours the loss of K^+. This could lead to hypokalemia (low levels of potassium in the blood), which could increase the toxicity of digoxin.

Pharmacodynamic interactions of NSAIDs

Platelet-related interactions—It is generally known that simultaneous administration of NSAIDs[3] increases the COX-1-mediated inhibition of thromboxane synthesis and hence the risk of gastrointestinal bleeding in a synergistic manner. A particular property of the acidic anti-inflammatory ibuprofen is its specific, reversible binding to COX-1, which prevents acetylsalicylic acid (ASA) from acetylating the serine residue at position 529 of the COX-1 protein. Irreversible and hence long-lasting inhibition of COX-1-mediated thromboxane A_2 synthesis by ASA can thus be prevented and the cardiac risk of patients with coronary heart disease can increase. Long-term clinical observations confirm these ex vivo observations, which appear also to hold for naproxen. Accordingly, patients with coronary heart disease on ASA prophylaxis should not take ibuprofen or naproxen on a regular basis.

Increased potassium retention

The combination of ACE inhibitors and potassium-sparing diuretics such as amiloride can increase potassium retention so strongly that life-threatening hyperkalemia ensues.

Interactions with the vascular system

NSAIDs can reduce the blood-pressure-lowering effect of ACE inhibitors. The main mechanism is via a reduction in glomerular perfusion[4] through a reduction of local prostaglandin E_2 synthesis with corresponding reactive secretion of renin. In a controlled clinical study, the blood pressure of healthy volunteers treated with lisinopril rose by 7 to 9 mmHg when they were given piroxicam. It was recently reported that these important interactions of NSAIDs are also true for AT1-receptor blockers. Low-dose ASA, on the other hand, appears to have no effect on arterial blood pressure. Nevertheless, doses of 300 mg ASA and higher can reduce the effects of ACE inhibitors.

Examples of typical additive and antagonistic pharmacodynamic interactions

Substance I	Substance II	Possible effect
Additive interactions		
NSAIDs	SSRI, phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
ACE inhibitors	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin syndrome
Tricyclic antidepressants	Low-potency neuroleptics	Increased anticholinergic effects
Quinolones	Macrolides, citalopram	QT-interval prolongation, torsade de pointes
Antagonistic interactions		
Acetylsalicylic acid	Ibuprofen	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug

Pharmacokinetic Interactions

Modifications in the effect of a drug are caused by differences in the absorption, transport, distribution, metabolism or excretion of one or both of the drugs compared with the expected behavior of each drug when taken individually. These changes are basically modifications in the concentration of the drugs. In this respect, two drugs can be homergic if they have the same effect in the organism and heterergic if their effects are different.

Absorption interactions

Changes in motility

Some drugs, such as the prokinetic agents increase the speed with which a substance passes through the intestines. If a drug is present in the digestive tract's absorption zone for less time its blood concentration will decrease. The opposite will occur with drugs that decrease intestinal motility.

- pH: Drugs can be present in either ionised or non-ionised form, depending on their pKa (pH at which the drug reaches equilibrium between its ionised and non-ionised form). The non-ionized forms of drugs are usually easier to absorb, because they will not be repelled by the lipidic bylayer of the cell, most of them can be absorbed by passive diffusion, unless they are too big or too polarized (like glucose or vancomycin), in which case they may have or not have specific and non specific transporters distributed on the entire intestine internal surface, that carries drugs inside the body. Obviously increasing the absorption of a drug will increase its bioavailability, so, changing the drug's state between ionized or not, can be useful or not for certain drugs.[5]

Certain drugs require an acid stomach pH for absorption. Others require the basic pH of the intestines. Any modification in the pH could change this absorption. In the case of the antacids, an increase in pH can inhibit the absorption of other drugs such as zalcitabine (absorption can be decreased by 25%), tipranavir (25%) and amprenavir (up to 35%). However, this occurs less often than an increase in pH causes an increase in absorption. Such as occurs when cimetidine is taken with didanosine. In this case, a gap of two to four hours between taking the two drugs is usually sufficient to avoid the interaction.

- **Drug solubility**: The absorption of some drugs can be drastically reduced if they are administered together with food with a high fat content. This is the case for oral anticoagulants and avocado.

- **Formation of non-absorbable complexes**

Chelation: The presence of di- or trivalent cations can cause the chelation of certain drugs, making them harder to absorb. This interaction frequently occurs between drugs such as tetracycline or the fluoroquinolones and dairy products (due to the presence of Ca^{++}).

Binding with proteins: Some drugs such as sucralfate binds to proteins, especially if they have a high bioavailability. For this reason its administration is contraindicated in enteral feeding. Finally, another possibility is that the drug is retained in the intestinal lumen forming large complexes that impede its absorption. This can occur with cholestyramine if it is associated with sulfamethoxazol, thyroxine, warfarin or digoxin.

Acting on the P-glycoprotein of the enterocytes: This appears to be one of the mechanisms promoted by the

consumption of grapefruit juice in increasing the bioavailability of various drugs, regardless of its demonstrated inhibitory activity on first pass metabolism.

Transport and distribution interactions

The main interaction[6] mechanism is competition for plasma protein transport. In these cases the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract these situations (by, for example, increasing plasma clearance), which means that they are not usually clinically relevant. However, these situations should be taken into account if other associated problems are present such as when the method of excretion is affected.

Interactions at the absorption level-formation of complexes

Complexes can considerably reduce the bioavailability of drugs. The bisphosphonates used in osteoporosis, such as alendronate, have a very low bioavailability of only 0.5% to 2%. Calcium ions in mineral water or milk reduce this markedly still further. Multivalent cations can also form complexes with tetracycline or quinolones and also reduce the bioavailability of levothyroxine; simultaneous intake of calcium-containing foods or neutralizing antacids containing aluminum or magnesium ions, must therefore be avoided. Recently, a reduction of the protective properties of alendronate with reference to avoiding hip fractures was observed when proton pump inhibitors were given at the same time.

Examples of interactions at the intestinal absorption level: selection of relevant substrates, inducers, and inhibitors of P-glycoprotein (ABCB1)

Group	Substance
Substrates	
Opioids	Loperamide, morphine
Antihypertensives	Aliskiren, carvedilol
Anticoagulants	Dabigatran
Cardiac glycosides	Digoxin
Immunosuppressants	Ciclosporin, tacrolimus, sirolimus
Protease inhibitors	Indinavir, saquinavir
Statins	Atorvastatin, lovastatin, simvastatin
Antineoplastic agents	Paclitaxel, anthracyclines, vinca alkaloids, etoposide, imatinib
Inducers	
Anticonvulsants	Carbamazepine (oxcarbazepine less so), phenytoin, phenobarbital, primidone
Tuberculostatics	Rifampicin
Antiretroviral	Efavirenz
St. John's wort extract	Hyperforin
Inhibitors	
Antimycotics	Itraconazole, ketoconazole
Calcium channel blockers	Diltiazem; felodipine; nicardipine; nifedipine; verapamil especially
Macrolide antibiotics	Erythromycin, clarithromycin, not azithromycin
HIV protease inhibitors	Indinavir; nelfinavir; ritonavir especially; saquinavir
Immunosuppressants	Ciclosporin
Antiarrhythmic drugs	Amiodarone, quinidine, propafenone

Metabolism interactions

Many drug interactions[7] are due to alterations in drug metabolism. Further, human drug-metabolizing enzymes are typically activated through the engagement of nuclear receptors. One notable system involved in metabolic drug interactions is the enzyme system comprising the cytochrome P450 oxidases.

CYP450

Cytochrome P450 is a very large family of haemoproteins (hemoproteins) that are characterized by their enzymatic activity and their role in the metabolism of a large number of drugs. Of the various families that are present in human beings the most interesting in this respect are the 1, 2 and 3, and the most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

The majority of the enzymes are also involved in the metabolism of endogenous substances, such as steroids or sex hormones, which is also important should there be interference with these substances. As a result of these interactions the function of the enzymes can either be stimulated (enzyme induction) or inhibited (enzyme inhibition).

Interactions at the cytochrome P450 enzyme level: selection of relevant substrates for which, when used in combination with inhibitors or inducers of the same enzyme, either increased effects and increased occurrence of unwanted effects, or reduced effects or loss of effect must be anticipated.

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	
Clozapine	**NSAIDs**	**Proton pump**	**Beta-blockers**	**Macrolide antibiotics**	**Statins**
Imipramine	Celecoxib	**inhibitors**	Metoprolol	Clarithromycin	Atorvastatin
Mexiletine	Diclofenac	Omeprazole	Propafenon	Erythromycin	Lovastatin
Naproxen	Ibuprofen	Lansoprazole	Timolol		Simvastatin
Tacrine	Naproxen			**Benzodiazepines**	
Theophylline	Piroxicam	**Miscellaneous**	**Antidepressants**	Alprazolam	**Anticoagulants**
		Amitriptyline	Amitriptyline	Diazepam	Apixaban
	Antidiabetics	Clomipramine	Clomipramine	Midazolam	Rivaroxaban
	Glipizide	Clopidogrel*	Desipramine	Triazolam	Phenprocoumon
	Tolbutamide	Cyclophosphamide*	Duloxetin		
		Diazepam	Imipramine	**Calcium channel**	**Miscellaneous**
	Angiotensin receptor	Phenytoin	Paroxetine	**blockers**	Aripiprazole
	blockers		Venlafaxine	Amlodipine	Buspirone
	Irbesartan			Diltiazem	Quinidine
	Lorsartan		**Antipsychotics**	Felodipine	Quinine
			Aripiprazole	Nifedipine	Ethinylestradiol
	Miscellaneous		Haloperidol	Nisoldipine	Imatinib
	Cyclophosphamide		Risperidone	Nitrendipine	Sildenafil
	Fluvastatin		Thioridazine	Verapamil	Tamoxifen
	Phenytoin				Vincristine
	Sulfamethoxazole		**Opioids**	**Immunosuppressants**	
	Torasemide		Codeine*	Ciclosporin	

Interactions with the most important cytochrome P450 enzymes: inhibitors and inducers (modified from

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
Inhibitors				
Fluoroquinolones	Amiodarone +	**SSRIs**	**SSRIs**	**HIV protease inhibitors**
Ciprofloxacin ++	Fluconazole ++	Fluoxetine	Duloxetin +	Indinavir ++
Ofloxacin	Isoniazide	Fluvoxamine	Fluoxetine ++	Nelfinavir ++
Levofloxacin			Paroxetine ++	Ritonavir ++
		PPIs		
Miscellaneous		Lansoprazole +	**Miscellaneous**	**Macrolides**
Amiodarone		Omeprazole +	Amiodarone	Clarithromycin ++
Cimetidine +			Buproprion	Erythromycin +
Fluvoxamine		**Miscellaneous**	Cimetidine	
++ Ticlopidine		Ketoconazole	Quinidine ++	**Azole antimycotics**
		Ticlopidine	Chlorphenamine	Fluconazole +
			Clomipramine	Itraconazole +
			Ritonavir	Ketoconazole ++
				Voriconazole
				Miscellaneous
				Aprepitant +, Amiodarone
				Cimetidine +
				Diltiazem
				Naringin + (in citrus fruits)
				Verapamil +

Anticoagulants—The most relevant interactions are those relating to drugs with a narrow therapeutic spectrum, such as ciclosporin or phenprocoumon. As already mentioned, vitamin K antagonists can trigger life-threatening hemorrhage and contribute to the incidence of medical drug-related hospitalizations. The cause could be interactions with older macrolide antibiotics such as erythromycin and clarithromycin, which inhibit cytochrome P450 3A4, important in the metabolization of phenprocoumon. Azithromycin shows

almost no interactions with the cytochrome P450 system. The calcium channel blockers verapamil and azole antimycotics can be highly potent CYP3A4 inhibitors. Ketoconazole inhibits the cytochrome P450 system so strongly that it is now used as a standard inhibitor in the clinical development of medical drugs, in order to test interactions with CYP3A4 among others.

Antidepressants-Selective serotonin reuptake inhibitors (SSRIs) are potent inhibitors of CYP2D6 (fluoxetine, paroxetine) and CYP1A2 (fluvoxamine). This has consequences for the co-administration of other drugs. In everyday practice, however, one must also watch out for interactions between antidepressants and common medical drugs such as certain beta-blockers. Fluoxetine and paroxetine also inhibit the metabolism of the beta-blocker metoprolol and can thus cause lowering of blood pressure, bradycardia, and other undesired effects.

Fluvoxamine, on the other hand, inhibits CYP1A2 and can thus increase the toxicity of theophylline or clozapine. A fatal interaction between fluoxetine and clozapine has also been reported.

The inhibition of CYP2D6 can also reduce the formation of active metabolites of codeine into morphine or tramadol into O-desmethyltramadol. It has been shown in large studies that the inhibition of CYP2D6-mediated activation of the anti-estrogen tamoxifen to endoxifen through SSRIs is associated with increased breast cancer mortality.

Quinolones-Quinolones such as ofloxacin and ciprofloxacin are primarily inhibitors of CYP1A2, which is also involved in metabolism of theophylline or clozapine. Simultaneous administration of, for example, ciprofloxacin and theophylline can lead to a rise in the plasma concentration of theophylline, with corresponding clinical symptoms of cardiac and gastrointestinal unwanted effects. The bioavailability of quinolones themselves can be markedly restricted if they are given at the same time as bivalent or trivalent cations, such as are contained in antacids or zinc or iron formulations.

Proton pump inhibitors (PPIs)—Proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, or rabeprazole inhibit cytochrome P450 2C19 (CYP2C19) to varying degrees. Omeprazole in particular (esomeprazole less so) is a substrate and inhibitor of CYP2C19.

Enzymatic inhibition

If drug A is metabolized by a cytochrome P450 enzyme and drug B inhibits or decreases the enzyme's activity, then drug A will remain with high levels in the plasma for longer as its inactivation is slower. As a result, enzymatic inhibition will cause an increase in the drug's effect. This can cause a wide range of adverse reactions. It is possible that this can occasionally lead to a paradoxical situation, where the enzymatic inhibition causes a decrease in the drug's effect: if the metabolism of drug A gives rise to product A_2, which actually produces the effect of the drug. If the metabolism of drug A is inhibited by drug B the concentration of A_2 that is present in the blood will decrease, as will the final effect of the drug.

Excretion interactions

Renal excretion

Only the free fraction of a drug that is dissolved in the blood plasma can be removed through the kidney. Therefore, drugs that are tightly bound to proteins are not available for renal excretion, as long as they are not metabolized when they may be eliminated as metabolites. Creatinine[8] clearance is used as a measure of kidney functioning but it is only useful in cases where the drug is excreted in an unaltered form in the urine. The excretion of drugs from the kidney's nephrons has the same properties as that of any other organic solute: passive filtration, reabsorption and active secretion. In the latter phase, the secretion of drugs is an active process that is subject to conditions relating to the saturability of the transported molecule and competition between substrates. Therefore, these are key sites where interactions between drugs could occur. Filtration depends on a number of factors including the pH of the urine, it having been shown that the drugs that act as weak bases are increasingly excreted as the pH of the urine becomes more acidic, and the inverse is true for weak acids. This mechanism is of great use when treating intoxications (by making the urine more acidic or more alkali) and it is also used by some drugs and herbal products to produce their interactive effect.

Bile excretion

Bile excretion[9] is different from kidney excretion as it always involves energy expenditure in active transport across the epithelium of the bile duct against a concentration gradient. This transport system can also be saturated if the plasma concentrations of the drug are high. Bile excretion of drugs mainly takes place where their molecular weight is greater than 300 and they contain both polar and lipophilic groups. The glucuronidation of the drug in the kidney also facilitates bile excretion. Substances with similar physicochemical properties can block the receptor, which is important in assessing interactions. A drug excreted in the bile duct can occasionally be reabsorbed by the intestines (in the enterohepatic circuit), which can also lead to interactions with other drugs.

Herb-Drug interactions

Herb-drug interactions[10] are drug interactions that occur between herbal medicines and conventional drugs. These types of interactions may be more common than drug-drug interactions because herbal medicines often contain multiple pharmacologically active ingredients, while conventional drugs typically contain only one. Some such interactions are clinically significant, although most

herbal remedies are not associated with drug interactions causing serious consequences. Most herb-drug interactions are moderate in severity. The most commonly implicated conventional drugs in herb-drug interactions are warfarin, insulin, aspirin, digoxin, and ticlopidine, due to their narrow therapeutic indices. The most commonly implicated herbs involved in such interactions are those containing St. John's Wort, magnesium, calcium, iron, or ginkgo.

Examples

Examples of herb-drug interactions include, but are not limited to: St. John's wort affects the clearance of numerous drugs, including cyclosporin, SSRI antidepressants, digoxin, ind inavir, and phenprocoumon. It may also interact with the anti-cancer drugs irinotecan and imatinib. Salvia miltiorrhiza may enhance anticoagulation and bleeding among people taking warfarin. Allium sativum has been found to decrease the plasma concentration of saquinavir, and may cause hypoglycemia when taken with chlorpropamide. Ginkgo biloba can cause bleeding when combined with warfarin or aspirin. Concomitant ephedra and caffeine use has been reported to, in rare cases, cause fatalities.

Mechanisms

The mechanisms underlying most herb-drug interactions are not fully understood. Interactions between herbal medicines and anticancer drugs typically involve enzymes that metabolize cytochrome P450. For example, St. John's Wort has been shown to induce CYP3A4 and P-glycoprotein in vitro and in vivo.

Underlying factors

It is possible to take advantage of positive drug interactions. However, the negative interactions are usually of more interest because of their pathological significance [11], and also because they are often unexpected, and may even go undiagnosed. By studying the conditions that favor the appearance of interactions, it should be possible to prevent them, or at least diagnose them in time. The factors or conditions that predispose the appearance of interactions include:

Old age: factors relating to how human physiology changes with age may affect the interaction of drugs. For example, liver metabolism, kidney function, nerve transmission or the functioning of bone marrow all decrease with age. In addition, in old age there is a sensory decrease that increases the chances of errors being made in the administration of drugs.

Polypharmacy: The use of multiple drugs by a single patient, to treat one or more ailments. The more drugs a patient takes the more likely it will be that some of them will interact. Genetic factors: Genes synthesize enzymes that metabolize drugs. Some races have genotypic variations that could decrease or increase the activity of these enzymes. The consequence of this would, on occasions, be a greater predisposition towards drug interactions and therefore a greater predisposition for adverse effects to occur. This is seen in genotype variations in the enzymes of cytochrome p450.

- **Drug dependent factors**:

Narrow therapeutic index: Where the difference between the effective dose and the toxic dose is small. The drug digoxin is an example of this type of drug. Steep dose-response curve: Small changes in the dosage of a drug produce large changes in the drug's concentration in the patient's blood plasma. Saturable hepatic metabolism: In addition to dose effects the capacity to metabolize the drug is greatly decreased.

1. Drug-drug Interactions

Drug-drug interactions result when two or more drugs react with each other. Such drugs can be from a combination of prescription drugs and/or over-the-counter (OTC) medications. Drugs with a narrow therapeutic range (little difference between therapeutic and lethal dose) are more likely to face incidents of serious drug interactions. **For example**: Taking digoxin with antibiotics like erythromycin or clarithromycin will increase the toxicity of digoxin because antibiotics affect the liver enzymes, causing digoxin to be metabolized (inactivated) slower. Similarly, the concurrent use of methotrexate and ibuprofen may result in increased methotrexate toxicity due to inhibition of kidney excretion by ibuprofen. The effectiveness of drugs may be reduced in situations where the action of one drug diminishes the action of the other. Some antibiotics reduce the effectiveness of oral contraceptive pills by impairing the bacterial flora responsible for recycling the hormone from the gut. Also, drugs like charcoal or magnesium carbonate should preferably not be taken at the same time as other drugs as they may impair absorption. Side effects of medications are intensified when drugs with the same effect are taken together. For instance, taking codeine (painkiller) with a cough syrup like procodin will increase the sedative effect. Aspirin, which is anti-platelet, increases the risk of bleeding when given together with warfarin, heparin or anti-depressants. There is also an increased risk of hepatotoxicity (liver damage) when isoniazid and paracetamol are used together.

Drug-food

This happens when food or beverage intake alters a drug's effect. For example, some statins (used to treat high cholesterol) can interact with grapefruit juice. If a person who takes one of these statins drinks a lot of grapefruit juice, too much of the drug may stay in their body, increasing their risk for liver damage or kidney failure. Another potential outcome of the statin-grapefruit juice interaction is rhabdomyolysis. This is when skeletal muscle breaks down, releasing a protein called myoglobin into the blood. Myoglobin can go on to damage the kidneys. The tobacco in cigarettes can also diminish the effectiveness of medications by increasing drug metabolism. Caffeine, which is found in tea, coffee,

soft drinks and chocolate and some medications, can increase the risk of theophylline (a drug to treat asthma) toxicity.

Drug-alcohol
Certain medications shouldn't be taken with alcohol. Often, combining these drugs with alcohol can cause tiredness and delayed reactions. It can also increase your risk for negative side effects.

Drug-disease
This interaction is when the use of a drug alters or worsens a condition or disease. Additionally, some medical conditions can increase the risk of side effects from specific drugs. For example, some decongestants that people take for colds can increase blood pressure. This is a potentially dangerous interaction for people with high blood pressure (hypertension). Another example is metformin (a diabetes drug) and kidney disease. People with kidney disease should use a lower dosage of metformin or not take it at all. This is because metformin can accumulate in the kidneys of people with this disease, increasing the risk of severe side effects.

Drug-laboratory
Some medications can interfere with specific laboratory tests. This can result in inaccurate test results. For instance, tricyclic antidepressants have been shown to interfere with skin prick tests used to determine whether someone has certain allergies.

Other factors in drug interactions
While it's important to educate yourself on your potential for drug interactions, understand that this information doesn't tell you everything you need to know. Just because a drug interaction can occur doesn't mean it will. Personal traits can play a role in whether a drug interaction will happen and if it will be harmful. Specifics about your drugs, including dosage, formulation, and how you take them, can also make a difference. The following factors of an individual's medical history influence possible drug interactions:

Genetics
Variations in individual genetic makeup can make the same drug work differently in different bodies. As a result of their particular genetic code, some people process certain medications more quickly or more slowly than others. This may cause the drug levels to go down or go up more than expected. Your doctor will know which drugs require genetic testing to find the correct dosage for you.

Weight
Some drugs are dosed according to how much a person weighs. Weight changes could affect dosage and also increase or decrease the risk of drug interactions. So if you have a substantial change in your weight, you could need a different dosage of some medications.

Age
As we age, our bodies change in many ways, some of which may affect how we respond to medications. The kidneys, liver, and circulation system may slow down with age. This can slow the breakdown and removal of drugs from our bodies.

Sex (male or female)
Differences between the sexes, such as anatomy and hormones, can play a part in drug interactions. For example, the recommended dose of zolpidem (Ambien) given to women was lowered to half the amount prescribed to men. This happened after research found that women were more likely to have high levels of the drug in their system in the morning, when it could impair activities like driving.

CONCLUSION

The systematic knowledge of drug interaction, in particular on the level of absorption, elimination, transport and drug metabolism may help to prevent adverse effects. Predicting pharmacodynamic interactions often demands a deeper understanding of the mechanisms of effect. Electronic prescribing systems are helpful. Pharmacokinetic interactions in particular are systematic. Knowledge of which enzymatic metabolic path is clinically relevant to the metabolization of a drug, whether it is the substrate of a drug transporter, and whether it inhibits or induces these proteins, makes it possible to predict pharmacokinetic interactions. Inhibitors of certain cytochrome P450 enzymes can influence the bioavailability of a whole group of drugs metabolized by the same enzyme, while inducers usually contribute to a loss of effectiveness.

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