Review Article

Drug Interactions

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ABSTRACT

The causes of negative drug effects and possible preventative measures have attracted a lot of attention over the last five years. The Institute of Medicine identified medication-related adverse events as the top cause of preventable death in the monograph to Error is Human. The negative effects of medication interactions have drawn attention, especially since many of these effects are foreseeable. Drug interactions continue to be a significant side effect of pharmaceutical management. It is obvious that the concurrent administration of another therapeutic substance or food can have a significant impact on how a medication acts pharmacologically. These interactions may lessen the therapeutic impact or raise the quantity and intensity of unwanted reactions. Numerous pharmaceutical, pharmacokinetic, or pharmacodynamics processes can be used by drugs to interact with one another. These interactions might be brought on by simultaneously prescribed therapeutic modalities, environmental factors, or the patient's particular habits, like diet, alcohol consumption, and tobacco use. Drug interactions are becoming more predictable, which emphasises how crucial it is for all healthcare professionals to comprehend their mechanisms, foresee when they might happen, and ideally avoid them.

Keywords: Drug-Drug interactions, Adverse drug reaction, Pharmacokinetic, pharmacodynamics, Cytochrome P450(CYP) family, ADME Pharmacological response.

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INTRODUCTION

A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease. Interactions between drugs (drug–drug interactions) may be beneficial or harmful. Harmful drug–drug interactions are important as they cause 10–20% of the adverse drug reactions requiring hospitalisation and they can be avoided. [1]

Elderly patients are especially vulnerable – with a strong relationship between increasing age, the number of drugs prescribed and the frequency of potential drug–drug interactions. Knowing how drug–drug interactions occur and how to manage them is an important part of clinical practice.

The ability of a drug to specifically target one receptor and produce a known physiological reaction is referred to as selectivity. Acetylcholine, for instance, causes smooth muscle spasms when it binds to the M3 receptors on the muscarinic tracheal smooth muscle.

Since the majority of receptors are already taken into consideration, the chance for selective drugs to bind with the intended receptor cells is reduced when freely binding receptors interact with agonists, chemicals that activate receptors, and antagonists, which inhibit/block activation. As a result, the drugs are more likely to bind to receptors other than the targeted receptor, producing effects that are different.

For instance, combining Zolpidem (a.k.a. Ambien), which affects GABA receptors, with alcohol causes this receptor to become overstimulated, which may result in unconsciousness. The likelihood of a drug-drug interaction (DDI) rises as more medications are taken. 15% of elderly people in the U.S. routinely use five or more prescription drugs or dietary supplements, and 36% are at risk of a serious drug-drug interaction.

Drug Interaction

Drug interaction refers as modification of response to one drug by another when they are administered simultaneously or in case of quick successful therapy and in conditions like polypharmacy

When a drug is used in conjunction with particular drug, foods, herbs, or other medications, or when it is used to treat particular medical conditions, the way the drug acts in the body changes. Medication interactions may alter a drug's effects or have unanticipated effects on the body. There are detrimental therapeutic effects when one drug (the offender) alters the concentration of another drug (the sufferer). [1]

REASON FOR DRUG INTERACTION

When two (or more) drugs, or a drug and a food, drink, or supplement, join, a drug interaction happens. Additionally, taking a medication while dealing with a particular medical situation can lead to a drug combination. for instance, taking a nasal decongestant while having elevated blood pressure is an example of how a drug interaction can alter how a drug works or have unintended negative effects. The two drugs involved in interaction are:

OBJECT DRUG: The drug for which the effect is altered (increased or decreased) is called as the object drug. Example: warfarin, fluoroquinolones, antiepileptic drugs.

PRECIPITANT DRUG: The drug that provokes the interaction is named as the precipitant drug. Example: Non-steroidal inflammatory drugs, antibiotics, rifampin.

Influence of drug interactions on distribution of drugs:

Object drug	Precipitant drug	Influence on Object drug
Anticoagulants	salicylates	Increased clotting time and increased risk of haemorrhage by the displacement of warfarin from its protein binding site.
Methotrexate	salcylicacid	Increased methotrexate toxicity.
Phenytoin	valproicacid	Phenytoin toxicity.
Sulfonylurea's (tolbutamide)	Insulin	Exerts therapeutic effects by displacing insulin from protein binding sites in pancreas; plasma and other regions resulting in its elevated levels.

Figure 1: Influence of drug interactions on distribution of drugs

RECENT DRUG WITHDRAWAL FROM MARKET:

i. Thioridazine, a common antipsychotic from the phenothiazine family, was extensively used to treat schizophrenia and psychosis but was discontinued globally in 2005 due to its severe cardiac arrhythmia-causing potential.

ii. The weight-loss medication lorcaserin, also known by the trade name Belviq, was sold. The hypothalamus, a part of the brain that is known to regulate appetite, contains a form of serotonin receptor called the 5-HT2C receptor, which is how it suppresses appetite. Due to an elevated risk of cancer found in Belviq users, it was authorised in 2012 and taken off the market in the United States in 2020.

iii. Ranitidine, which was formerly marketed under the brand name Zantac among others, was once a widely used drug used to lessen the generation of stomach acid. It was applied to the therapy of Zollinger-Ellison syndrome, gastroesophageal reflux disease, and peptic ulcer disease. Due to its carcinogenic nature, ranitidine was taken off the market in the United States as well as Australia and the European Union in April 2020. In a population study conducted across the country in 2022, it was discovered that ranitidine significantly increased the chance of developing liver, lung, gastric, and pancreatic cancer by 22%, 17%, 26%, and 35%, respectively. It resulted in a 10% overall cancer risk rise, p 0.001.

iv. Flupirtine is an amino pyridine that acts as a centrally acting non-opioid analgesic. It was first used as an analgesic for both acute and chronic pain, but in 2013 the European Medicines Agency restricted its use to acute pain, for no longer than two weeks, and only for individuals who are unable to use other painkillers due to liver toxicity. The European Medicines Agency recommended in March 2018 that Flupirtine's marketing authorizations be revoked due to the continued occurrence of severe liver injury cases, including liver failure.

CLASSIFICATION

FIRST CLASSIFICATION

Based on clinical importance, drug interaction can be classified as:

i. Beneficial Drug Interaction: Few drugs have positive impacts when they interact with other drugs. Some of these advantages include potentiation or synergisms. Some drugs are purposefully used to increase the effects of other drugs or to lessen their undesirable effects. 2 Examples include the combinations of sulpha methaxozole and trimethoprim as well as carbidopa and levodopa. There are numerous formulations on the market that make use of these advantageous effects, including combinations of B. blockers and diuretics and estrogens and progestogens as powerful antibiotics and contraceptives.

ii. Adverse interactions: When two or more drugs are taken at the same time, they may have an impact on one another that either intensifies or lessens the effect that would have been created by any one of the drugs taken alone. The encounter is typically referred to as antagonistic when the intensity is reduced. As an illustration, consider rashes, jaundice, anaemia, a drop in white blood cells, and kidney injury. 2

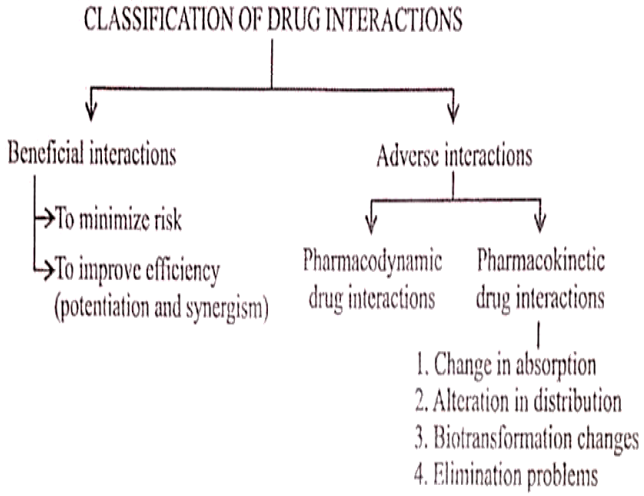

Figure 2: Classification of drug interactions

SECOND CLASSIFICATION

PHARMACOKINETIC DRUG INTERACTIONS

Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolised and excreted (the so called ADME interactions).

I. Drug absorption interactions

(a) Effects of changes in gastrointestinal pH: Drugs can be present in either ionized or non-ionized form, depending on their pKa (pH at which the drug reaches equilibrium between its ionized and non-ionized form). The non-ionized forms of drugs are usually easier to absorb because they will not be repelled by the lipidic bilayer of the cell, most of them can be absorbed by passive diffusion, unless they are too large or polarized (like glucose or vancomycin), in which case they may or may not have specific and non-specific transporters distributed on the entire intestine internal surface, that carries drugs inside the body.3 Obviously increasing the absorption of a drug will increase its bioavailability, so, changing the drug's state between ionized or not can be useful for certain drugs. 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 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 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. [3]

(b) Adsorption chelation and other complexing mechanisms: 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 sulfamethoxazole, 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.

(c) Changes in gastrointestinal motility: Drugs that change how quickly the stomach empties may have an impact on absorption because the majority of medications are mostly taken in the upper portion of the small intestine. Propantheline, for instance, slows down gastric emptying and decreases paracetamol (acetaminophen) absorption; metoclopramide, on the other hand, has the opposite impact; see "Paracetamol (Acetaminophen)+Domperidone or metoclopramide,". The overall quantity of drug absorbed is unaffected, though.

(d) Induction or inhibition of drug transporter proteins: Drug transporter proteins, which eject drugs that have diffused across the gut lining back into the gut, restrict the oral bioavailability of some medications. Digoxin is a substrate of P-glycoprotein, which is currently the most well-studied drug transporter. Drugs that activate this protein, such as rifampicin (rifampin), may decrease the bioavailability of digoxin.

(e) Malabsorption caused by drugs: Neomycin results in a malabsorption condition that resembles non-tropical sprue. The result is that many medications, such as digoxin and methotrexate, have their digestion impaired.

II. Drug distribution interactions

(a) Protein-binding interactions: Drugs are quickly circulated throughout the body by the circulation after ingestion. While many medications are transported with some of their molecules in solution and the remainder attached to plasma proteins, especially the albumins, some medications are completely dissolved in the plasma water. Although the degree of this binding differs greatly, some drugs are very strongly bound. For instance, at serum concentrations of 0.5 milligrams, only four out of every 1000 molecules of dicoumarol are still unbound. Additionally, some drugs, like digoxin, can attach to the heart muscle tissue and others, like albumin in the interstitial fluid, can become bound to albumin. Those that are bound form a circulating but inactive reservoir that, in the case of medications with a low extraction ratio, is momentarily shielded from metabolism and excretion. Only the unbound molecules stay free and pharmacologically active.

(b) Induction or inhibition of drug transporter proteins: Drug transporter proteins like P glycoprotein are now widely acknowledged to have a restriction on drug distribution to the brain and some other tissues like the testicles. When drugs have quietly diffused into cells, these proteins actively transport them out. As a result, medications that inhibit these transporters may cause more drug substrates to enter the brain, which may either enhance negative CNS effects or have positive effects.

Drugs affecting or metabolised by the cytochrome P450 iso enzyme CYPIA2

	Object drug	Precipitant drug
Inhibitors	Cimetidine Fluoroquinolones: ciprofloxacin, enoxacin Fluvoxacin, Methoxsalen mexiletine	Oestrogens Rofecoxib Tacrine Tiabendazole Ticlopidine Zileuton (2)
Inducers	Barbiturates Phenytoin	Tobacco smoke
Substrate	Alosetron Caffeine Melatonin Olanzapine Ropinirole Ropivacaine	Theophylline Tizanidine Tricyclic antidepressant: amitriptyline, clomipramine, imipramine Triptans: frovatriptan, zolmitriptan *R*- warfarin

Figure 3: Drugs affecting or metabolised by the cytochrome P450 iso enzyme CYPIA2

III. Drug Metabolism

Changes in drug metabolism are the most important causes of unexpected drug interactions. These occur by changing drug clearance or oral bioavailability. There are several enzyme families involved in drug metabolism, and the cytochrome P450 (CYP) enzyme family is the most important.

Inhibition of a cytochrome P450 enzyme increases the concentration of some drugs by decreasing their metabolism. For example, clarithromycin is a strong inhibitor of CYP3A-catalysed simvastatin metabolism, thus increasing the risk of myopathy. [3] Drug inhibition of cytochrome P450 enzymes is also used therapeutically. For example, ritonavir, a strong inhibitor of CYP3A, reduces metabolism of other protease inhibitors thus increasing their effectiveness in treating HIV (so called 'ritonavir-boosted' regimens).

Induction of a cytochrome P450 enzyme decreases the concentration of some drugs by increasing their metabolism. For example, carbamazepine is a strong inducer of CYP3A that increases the metabolism of the combined oral contraceptive, thus increasing the risk of unwanted pregnancy. [3]

(a) **Genetic factors in drug metabolism:** Growing knowledge of genetics has revealed that some cytochrome P450 isoenzymes are susceptible to "genetic polymorphism," which essentially means that some members of the community have a variant of the isoenzyme with different (usually subpar) activity. The best-known instance of this is CYP2D6, for which a tiny percentage of the population has a variant with low activity and is characterised as a poor or slow metabolizer; which category any specific person belongs to is genetically determined.

(b) **Cytochrome P450 isoenzymes and predicting drug interactions:** Because it is frequently possible to explain why and how some drugs interact by performing in vitro tests with human liver enzymes, it is fascinating to know which specific isoenzyme is responsible for the metabolism of drugs.[4] It is not surprising that rifampicin lowers cyclosporine levels and ketoconazole raises them because cyclosporine is metabolised by CYP3A4, and rifampicin (rifampin) is a known, powerful inducer of this isoenzyme, whereas ketoconazole inhibits its activity.

IV. Drug excretion interactions

(a) Changes in urinary pH: Similar to how drugs are absorbed in the stomach, passive reabsorption of drugs is influenced by how much of the drug is present in the non-ionized lipid-soluble form, which in turn is influenced by the drug's pKa and the pH of the urine. Only the non-ionized version can diffuse back through the lipid membranes of the tubule cells because it is lipid-soluble. Therefore, at high pH levels (alkaline). However, the bile salt export pump (ABCB11) molecules, which are unable to diffuse into the tubule cells and will instead there- is known to be inhibited by a variety of drugs including cyclosporine, glib fore remain in the urine and be eliminated from the body. Weakly acid drugs (pKa 3 to 7.5) largely exist as ionised lipid-insoluble drug interactions are still unclear. The opposite will occur, along with bosentan. This is especially true for weak bases with pKa values between 7.5 and 10.5, 14 when this pump is inhibited. As a result, pH changes that result in more drug in the ionised state (alkaline urine for acidic drugs, acid urine for basic drugs) will result in more drug loss. Alternatively, raising their retention will result from shifting the pH in the other way.[4]

(b) Changes in active renal tubular excretion: Drugs can compete with one another for excretion if they use the same active transport mechanisms in the renal tubules. Probenecid, for instance, lowers the elimination of penicillin and other medications. Probenecid suppresses the renal secretion of many other anionic drugs by organic anion transporters, according to growing knowledge of drug transporter proteins in the kidneys (OATS) Possible side effects of probenecid include renal ABC transporter inhibition. P-glycoprotein, an ABC transporter that is also found in the kidneys, may be affected by drugs by changing renal drug elimination.

Changes in renal blood flow: Renal vasodilatory prostaglandin synthesis contributes to the regulation of blood flow through the kidney. The renal excretion of some medications may be decreased if the synthesis of these prostaglandins is blocked. The increase in serum lithium observed with some NSAIDs, as described in "Lithium+NSAIDs," is an interaction for which this is the proposed cause.

Biliary excretion and the entero-hepatic shunt:

Enterohepatic re circulation: Many medications are eliminated in the liver, either unaltered or conjugated (for example, as the glucuronide to increase their water solubility). Some of the conjugates are converted by the gut bacteria to the parent compound and then reabsorbed. This recycling process lengthens the time the drug remains in the body, but if an antibacterial is present, the drug is not recycled and is lost more rapidly. This may help to explain the infrequent failure of hormonal contraceptives that can result from taking penicillin or tetracycline at the same time.[4]

Drug transporter proteins: The extraction and secretion of pharmaceuticals into the bile by the liver is mediated by a variety of drug transporter proteins, including those from the ABC family and the SLC family (see Drug transporter proteins). Although the significance of many of these to drug interactions is still debatable, it is known that a number of medications, such as cyclosporine, glibenclamide, and bosentan, block the bile salt export pump (ABCB11).

Object Drug (s)	Precipitant Drug (s)	Influence on Object Drug (s)
Metabolism Interactions		
1. Enzyme Induction		
Corticosteroids, oral contraceptives, coumarins, phenytoin, tolbutamide, tricyclic antidepressants	Barbiturates	Decreased plasma levels; decreased efficacy of object drugs
Corticosteroids, oral contraceptives, theophylline, cyclosporin	Phenytoin	Decreased plasma levels; decreased efficacy of object drugs
Oral contraceptives, oral hypoglycemics, coumarins	Rifampicin	Decreased plasma levels; decreased efficacy of object drugs
2. Enzyme Inhibition		
Tyramine rich food (cheese, liver, yeast prodcuts)	MAO Inhibitors (phenelzine , pargyline)	Enhanced absorption of unmetabolised tyramine; increased pressor activity; potentially fatal risk of hypertensive crises
Drugs that undergo extensive first-pass hepatic metabolism (e.g. Propranolol, calcium channel blockers, etc.)	Grape fruit juice	Enhanced absorption of drugs; increased risk of toxicity.
Folic acid	Phenytoin	Decreased absorption of folic acid due to inhibition of an enzyme responsible for its absorption
Tricyclic antidepressants	Chlorpromazine, haloperidol	Increased plasma half-life of tricyclics; increased risk of sudden death from cardiac disease in such patients.
Coumarins	metronidazole, Phenylbutazone	Increased anticoagulant activity; risk of haemorrhage
Oral hypoglycemics	Phenylbutazone, sulphaphenazole, chloramphenicol	Hypoglycemia may be precipitated
Alcohol	Disulphiram, metronidazole, tinidazole	Disulphiram like reactions due to increase in plasma acetaldehyde levels
AZT, mercaptopurine	Xanthine oxidase inhibitors (Allopurinol)	Increased toxicity of antineoplastics
Alcohol, benzodinzepines, warfarin, phenytoin, theophylline, phenobarbital	Cimetidine	Increased blood levels of object drugs

Object Drug (s)	Precipitant Drug (s)	Influence on Object Drug (s)
Excretion Interactions		
1. Changes in Active Tubular Secretion		
Penicillin, cephalosporin, Nalidixic acid, PAS, Methotrexate, Dapsone	Probenecid (acid)	Elevated plasma levels of acidic drugs; risk of toxic reactions
Procainamide	Cimetidine (base)	Increased plasma levels of basic object drugs; risk of toxicity
Acetohexamide	Phenylbutazone	Increased hypoglycemic effect
2. Changes in Urine pH		
Amphetamine, tetracycline, quinidine	Antacids, thiazides, Acetazolamide	Increased passive reabsorption of basic drugs; increased risk of toxicity
3. Changes in Renal Blood Flow		
Lithium bicarbonate	NSAIDS (inhibitors of prostaglandin synthesis; the latter control renal blood flow partially by vasoconstriction)	Decreased renal clearance of lithium; risk of toxicity

Figure 4: Pharmacokinetic interactions

PHARMACODYNAMIC DRUG INTERACTION

When one drug in a combination regimen's pharmacological effect is altered by another, this is referred to as a pharmacodynamics drug-drug interaction (DDI). Even though these words are frequently misused, DDIs are frequently categorised as additive, antagonistic, or synergistic in character.[5]

Drug-drug interactions (DDIs) occur when one substance alters the way another one functions. Drug responses can be pharmacokinetic (PK) or pharmacodynamic (PD).

In contrast to PK interactions, which happen when one drug modifies the absorption, distribution, metabolism, or elimination (ADME) of another, PD DDIs happen when the pharmacological effect of one drug is impacted by that of another.

Additive or synergistic effect:

• PD DDIs are typically divided into synergistic, additive, or antagonistic categories, despite the fact that these words are frequently misused. The overall effect of a drug combination is equivalent to the sum of the pharmacological effects of each individual agent, according to the additivity idea.[5]

Antagonistic or synergistic effect:

• A drug combination is said to be synergistic when its overall impact is greater than additive; antagonistic when it is less so. PD DDIs may be applied in a beneficial or harmful manner, with or without intention.

• A response the body has to two or more drugs that interact negatively with one another. Drug antagonists may stop or reduce the effectiveness of one or more medicines. For instance, when fluoroquinolones and macrolides like erythromycin are combined, QT delay may happen.

THIRD CLASSIFICATION

Drug-Drug Interactions

Any reaction between two (or more) medications, or between a drug and a supplement, food, or drink, is referred to as a drug interaction. A drug combination can also result from taking a medication while having a specific medical condition.[5]

For instance, if you have high blood pressure, consuming a nasal decongestant may result in an undesirable side effect.

Food-Drug Interaction

Food-drug interactions are defined as alterations of pharmacokinetics or pharmacodynamics of a drug or nutritional element or a compromise in nutritional status as a result of the addition of a drug.[6]

Examples of food drug interaction:

Drug Class	Food that Interacts	Effect of the Food	What to Do
Analgesic acetaminophen (Tylenol)	Alcohol	Increases risk for liver toxicity	Avoid alcohol
Antibiotic			
⇨ tetracyclines	⇨ Dairy products; iron supplements	⇨ Decreases drug absorption	⇨ Do not take with milk. Take 1 hour before or 2 hours after food/milk.
⇨ amoxicillin, penicillin, zithromax, erythromycin	⇨ Food	⇨ Decreases drug absorption	⇨ Take 1 hour before or 2 hours after meals.
⇨ nitrofurantoin (Macrobid)	⇨ Food	⇨ Decreases GI distress, slows drug absorption	⇨ Take with food or milk.
Anticoagulant warfarin (Coumadin)	Foods rich in Vitamin K	Decreases drug effectiveness	Limit foods high in Vitamin K: liver, broccoli, spinach, kale, cauliflower, and Brussels sprouts
Anticonvulsant phenobarbital, primidone	Alcohol	Causes increased drowsiness	Avoid alcohol
	Vitamin C	Decrease in drug effectiveness	Avoid excess vitamin C
Antifungal griseofulvin (Fulvicin)	High-fat meal	Increases drug absorption	Take with high-fat meal

Figure 5: Food drug interaction

Examples: Consuming foods rich in vitamin K, such as green, leafy vegetables, can lessen how well aspirin thins blood. A consistent daily intake of green leafy veggies will lessen this interaction. Milk, yoghurt, and cheese are dairy items that reduce the absorption of antibiotics. To prevent this interaction, try to consume a meal one to two hours before taking these.

Grapefruit juice: when interacts with drug, inactivates metabolizing intestinal enzyme resulting in enhanced activity and possible toxicity.it is used to treat seizures, depression, high blood pressure, high cholesterol, and pain.[6]

Caffeine: increase adverse effects of stimulants such as amphetamines, methylphenidate, theophylline, causing

nervousness, tremor, insomnia. Counters the antianxiety effect of tranquilizers.

Alcohol: effects oral diabetic medications or insulin. Low blood sugar results from these medications' effects being prolonged by alcohol. Because there is a greater risk of severe liver damage when alcohol is combined with moderate painkillers containing acetaminophen, this combination should be avoided. Benadryl and other antihistamines shouldn't be taken with booze because doing so will make you drowsier.[17]

Pineapple: Pineapple contains a compound known as bromelain. Fresh pineapple should not be combined with Amoxicillin or tetracycline antibiotics. When fresh pineapple is combined with these types of medications, it can increase the amount of medication absorbed by the body. In this case, it might increase the side effects of the medications. If you are taking a prescription blood thinner, be careful with bromelain that could affect the body's blood clotting abilities.

Factors associated with food drug interaction

High risk patients: mostly among, adults at age 65 and older, 40% are taking five or more medications. These older adults, who are typically taking multiple medications for multiple conditions, are among those at high risk for drug interaction.

Insufficient nutritional status: certain drugs may increase or decrease or prevent nutrient absorption in the gut. Drugs may speed up the metabolism of certain nutrients, resulting in higher dietary requirements of that particular nutrient.

People who are multiple and prolonged drug therapy: the simultaneous use of two or more drugs to kill all the pathogens and prevent resistant pathogens from growing.

Example: for treatment of tuberculosis. Synergism: the use of two or more drugs that work together "team up" and the effect on pathogens is better than either drug alone. Antagonism: the use of two or more drugs that work against each other and the effect on pathogens is less than either drug alone.

People having impaired renal and hepatic failure: Hepatorenal syndrome (HRS) is a form of impaired kidney function that occurs in individual with advanced liver disease. Individuals with hepatorenal syndrome do not have any identifiable cause of kidney dysfunction and the kidneys themselves are not structural damaged.

HERB DRUG INTERACTIONS

Herbal drugs	Biological source	Interaction reported or suspected
Ginkgo	*Ginkgo biloba*	Concurrent use of ginkgo and nonsteroidal antiinflammatory agents may result in an increased risk of bleeding and with warfarin causes bleeding. (Meisel et al., 2003)
Garlic	*Allium sativum*	Concurrent use of garlic and anticoagulants result in increased risk of bleeding. (Legnani et al., 1993)
Ginger	*Zingibar officinale*	Concurrent use of ginger and anticoagulants may result in increased risk of bleeding, sulfa guanidine enhance absorption. (Kruth et al., 2004)
Ginseng	*Panax ginseng*	Concurrent use of ginseng and antidiabetic agents may result in increased risk of hypoglycemia. (Vuksan et al., 2000)
St. John's wort	*Hypericum perforatum*	Concurrent use of digoxin and St John's wort may result in reduced digoxin efficacy. (Hennessy et al., 2003)
St. John's wort	*Hypericum perforatum*	Warfarin (cause bleeding); serotonin-uptake inhibitors (cause mild serotonin syndrome); indinavir (decreased bioavailability); digitoxin, theophylline, cyclosporin, phenprocoumon and oral contraceptives reduces bioavailability. (Cupp et al., 1999)
Rhubarb	*Rheum officinale*	Cardiac glycosides and anti-arrhythmic agents potentiates by reducing potassium via laxative effect. (Westendorf, 1993)
Astragalus	*Astragalus membranaceus*	Cyclosporine, azathioprine, methotrexate impair immuno-suppressive effects.
Licorice	*Glycyrrhiza uralensis*	Corticosteroids and thiazide diuretics potentiating; digitalis or other cardiac glycosides increases sensitivity (Mu et al.,2006)
Ma-huang	*Ephedra sinica*	With MAO inhibitors cause hypertension; cardiac glycosides or halothane react to produce cardiac arrhythmia; caffeine intensify cardiovascular side effects.
Aloe	*Aloe ferox*	Cardiac glycosides and antiarrhythmic agents potentiates by reducing potassium via laxative effect (Westendorf, 1993)

Figure 6: Herbal Drug Interactions

St. John wort:

Hypericum perforatum, sometimes known as St. John's wort, is a plant that has been heavily promoted as a "natural" antidepressant. This herb is frequently given in Germany for a variety of psychopathologic diseases that include anxiety and depression. The sale of herbal items is permitted20.

•St. John's wort may lessen the effects of some narcotics when taken together. Taking the supplement with drugs may lengthen the amount of time they produce sleep and pain relief.

St. John's wort is a native of Europe, and it has yellow blooms with stars on them. Although it's frequently used to treat depression, it can seriously infect several medications. The active component of St. John's wort is said to be hypericin, a supposedly effective monoamine oxidase (MAO) inhibitor. Dosing is based on the hypericin content of St. John's wort.[7]

•Studies have shown that St. John's wort extract inhibits serotonin, dopamine and norepinephrine reuptake in vitro. Consequently, it would be prudent to avoid the concomitant use of St. John's wort and antidepressants until further information is available.

Given that the half-life of hypericin is 24 to 48 hours, a conservative recommendation would be to wait until two weeks after a patient has stopped taking St. John's wort and then prescribe an antidepressant. However, if a patient needs to be started on an antidepressant expeditiously, a relatively long "washout period" may not be practical.

Despite the paucity of evidence for food and drug interactions with St. John's wort, patients who use this herb and then begin taking antidepressants or other serotonergic drugs should be observed carefully for adverse effects.

•• Side effects of St. John's wort include dry mouth, dizziness and confusion. In one open study of more than 3,000 patients, gastrointestinal symptoms, allergic reactions and fatigue were reported by 0.6 percent, 0.5 percent, and 0.4 percent of patients, respectively.

•Phototoxicity manifested as elevated, itching, erythematous lesions have also been reported in association with the use of St. John's wort. Neuropathy associated with sun exposure is another manifestation of phototoxicity.[7]

TOXICITY OF HERBAL MEDICINES

1.Self-treatment

▪ At ill 13% Herbal medicines are easily available in market and can be purchased without prescription. These products are advertised on media as a miracle treatment without any side effects to attract people that are fed up with side effects or lost hope for being cured.

•The patients who like to play safe game are attracted in a manner that they are allowed to continue their regular medicines along with herbal treatment. Even persons caring about their health start herbal treatment to remain healthy proving the proverb "Prevention is better than cure." As a result, a large number of people are attracted towards herbal medicines and they start self-treatment.[8]

2. Unqualified practitioners

•With the exception of those nations where laws and regulations for herbal practitioners are in place and are being followed, unqualified practitioners are prescribing alternative medicines to patients with a variety of conditions throughout a vast portion of the world. Medical professionals are given extensive training in the human body, medications, their mechanisms of action, pharmacology, and case studies before being licenced to practise.

• Despite the fact that some universities now offer Alternative Medicine Degree Programs with Highly Qualified and Experienced Faculty, which is a good source of herbal practitioners, 50% of herbal practitioners worldwide are unqualified and start practising after following in the footsteps of their ancestors, such as the son of a farmer becoming a farmer, reading some books about herbal medicine, taking a 6-month online course about herbal medicine, etc.[8]

• People in less developed nations are drawn to these charlatans for economic reasons and begin using herbal remedies. Even these unqualified practitioners are unaware of the hazardous consequences of herbal remedies, so even if the patient complains, they are unable to correct their error.

3. Sub-standard product

There are a lot of low-quality herbal products on the market. The cause is that these goods are not adequately checked for quality prior to marketing. Because of faulty plant identification by the collector, the use of adulterants in place of the actual plant, or improper preservation of plant material, some contain less active substance than others, and some do not contain any at all, losing their efficacy.

• Herbal goods occasionally include ingredients that aren't listed on the label, like non-herbal ingredients, minerals, heavy metals, and the addition of a specific medicinal product. They may occasionally contain pesticides and poisons, which is far riskier and one of the main causes of adverse consequences after ingesting herbal medicines.[9]

4. Improper intake

Allopathic medications are marketed following thorough testing and trials, and their dosage is set based on the patient's age and weight. The pamphlet includes a list of all potential negative effects. But when it comes to natural remedies, no such protocols are followed.

• Several herbal remedies are regarded as dietary supplements, and the recommended dosage is not stated. The medication is not packaged with a measuring cup or spoon like allopathic syrups are. The same dose is often given to people of various ages and weights. Businesses who sell these products mislead consumers by claiming that their goods are completely devoid of negative consequences. Even though a time frame is not specified, some continue for months or years, which over time may be detrimental to human health

DRUG CLASS	EXAMPLES
Antiarrhythmic	amiodarone
Anticoagulant	warfarin
Antiepileptic	phenytoin
Antineoplastic	sunitinib
Aminoglycoside antibiotic	gentamicin
Immunosuppressants	tacrolimus

Figure 7: Drug class frequently interact with example

METHODS TO IDENTIFY DRUG INTEREACTIONS AND MANAGEMENT OF DRUG INTEREACTIONS:

1. DRUG INTERACTION PROBABILITY SCALE(DIPS):

The DIPS was created to evaluate the likelihood that a possible drug interaction and an observed event are causally related. The Naranjo scale served as the foundation for DIPS, but it was altered to take into account the crucial distinctions between an adverse drug event and one brought on by a drug-drug interaction. Based on the responses to a series of questions designed to assess a potential drug interaction, the DIPS adds or deducts points.

• Understanding the pharmacologic, pharmacokinetic, and pharmacodynamic characteristics of both the object drug and the precipitant drug involved in the interaction is necessary for applying the DIPS to a probable drug interaction.[9]

Figure 8: DIPS = Drug Interaction Probability Scale;

Example of Completed DIPS Form		
DIPS questions	**Answer or Score**	**Comments**
1. Are there previous credible reports of this interaction in humans?	NA/0	At the time of the report, 1 case report purporting an interaction and 1 report of 6 cases without an interaction had been published. Neither report met the criteria for a credible report; both are disregarded as evidence in this case.
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	No/-1	Cyclosporine is a substrate for CYP3A4 and P-glycoprotein. Azithromycin is not known to inhibit CYP3A4 or P-glycoprotein.
3. Is the observed interaction consistent with the known interactive properties of object drug?	NA/0	Since no known properties of azithromycin affect cyclosporine, the answer is NA.
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	Yes/1	The time course of the change in cyclosporine concentrations would be consistent with a change in its elimination.
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (If no dechallenge, use “Unknown or NA” and skip Question 6).	Yes / 1	Stopping azithromycin did coincide with a fall in the concentration of cyclosporine.
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	No / 0	No rechallenge was attempted.
7. Are there reasonable alternative causes for the event?	Yes / –1	As noted by the authors, alternative reasons existed (e.g., cytokine-induced inhibition of CYP3A4 metabolism) that could lead to reduced cyclosporine metabolism.
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	Yes / 1	Cyclosporine concentrations were measured and varied appropriately with the administration and discontinuation of azithromycin.
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	NA / 0	There was no other evidence of the interaction except elevated cyclosporine concentration.
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	NA / 0	There was no change in the precipitant drug dose.

NA = not applicable.

SOFTWARES USED FOR CHECKING DRUG INTERACTIONS:

¡ Lexicomp:

Pharmacists working in community pharmacies or hospitals can use Lexicomp as a drug reference tool. Lexicomp's user-friendly navigation, medication monographs, and drug interaction checks can help pharmacists work more efficiently and effectively across the board of the pharmacy. This tool is made to rapidly and effectively connect you to medication-related information, giving pharmacists, doctors, and nurses timely and pertinent drug information.[10]

Lexicomp is a go-to tool for medical professionals to learn everything they need to know about a particular medication. Its purpose is to provide them with this information. You can download drug databases with full access to the app, which are available in a variety of languages and include details on pill identification, dosages, interactions, contraindications, pharmacogenomics, paediatric drugs and dosages as well as IV medication compatibility, concise adult and paediatric information handouts for patients, and toxicology of household products.

One of the most thorough pharmacological databases, the Lexicomp app provides extensive information and content about drugs. The information can also be directly printed or forwarded via email from the app.

¡¡. Micromedex:

•An indexing database called Micromedex gives users access to tertiary literature in full-text. Information about pharmaceuticals, toxicity, illnesses, acute care, and alternative medicine is provided in this tertiary literature without bias and with references.

•More than thirty drug-related items are included in Micromedex 2.0, including the Physician's Desk Reference, RED BOOK (drug pricing), patient care handouts, one herbal monograph source, three books of over-the-counter and prescription drug monographs (one focused on paediatric and neonatal patients), poisoning or toxicology, laboratory tests, evidence-based information on diseases, new drugs and drugs in development, books focusing on pregnancy and lactation, poisoning or toxicology, new drugs and drugs.[10]

•Comparative materials created by their editorial team, creative displays, and deep connecting between things are just a few of Micromedex's distinctive qualities.

TEXTBOOKS USED FOR CHECKING DRUG INTERACTIONS:

Stockley's Drug Interactions:

Stockley's Drug Interactions aims to provide busy medical professionals with information about drug interactions without requiring them to conduct time-consuming literature searches or complete assessments of the articles themselves.

So, the following are the pertinent questions that this book aims to address:

Are there known interactions between the pharmaceuticals and chemicals in issue, or is the connection purely hypothetical and conjectural?

• What severity is there if they do interact?

• Was it described more than once or just once?

• Are all patients impacted, or are just some?

• Should these two substances be avoided entirely, or is there a way to mitigate their interaction?

• What safer alternatives are available in their place?

This book contains more than 3100 monographs that all follow the same format and are separated into the following sections:

• A synopsis or abstract for quick reading.

• Clinical evidence that includes one, two, or more illustrations of the interaction, followed by the majority or all of the other available clinical data that supports it.

Mechanism, in a nutshell.

• Significance and management, a succinct presentation intended to facilitate quick clinical judgement. For instance:

– If so, has the interaction been established?

- What is the prevalence?

How significant is it?

How can it be controlled?

– And what, if any, are the alternatives that do not interact?

References, a complete list of all pertinent references. A very good estimate of the depth of the documentation is provided by the length of the references list. A lengthy list denotes a thoroughly documented encounter, while a condensed list denotes inadequate documentation.[10]

Just because there is insufficient information or there is no need to be more broad, some of the monographs feature fewer subsections rather than the more typical five. Due to the difficulties in applying them to monographs that cover multiple pairs of drug-drug interactions, the monographs do not include the drug interaction Hazard/Severity ratings as used in the electronic Stockley Interactions Alerts. However, what is written in each monograph should speak for itself.[11]

ANTICIPATING DRUG INTERACTIONS IN INDIVIDUAL PATIENTS:

A stepwise approach: Use mnemonic "THOUGHT"

T -Take a good medications history:

Use mnemonic "AVOID Mistakes" [Allergies, Vitamins and herbs, Old drugs/OTC, Interactions, Dependence,Mendel (polymorphisms)]

H - High risk patients (multiple meds, old, frail, ill)

O - Optimize therapy by decreasing number of drugs, use "low-problem" agents

U - Use interactions guides (pocket reference, computerized data banks, experts)

G - Give counsel about OTC and "herbals"

H - Have a monitoring plan to look for potential problems

T - Time, remember some interactions will take time to occur; some are rapid

ROLE OF PHARMACIST:

Five rules to manage potential DDI in Clinical effects

Class 1: Avoid combination (risk of combination outweighs benefit)

Class 2: Usually avoid combination (use only under special circumstances)

Interactions for which there are clearly preferable alternatives to one or both drugs

Interactions to avoid using an alternative drug or other therapy unless the benefit is judged to outweigh the increased risk

Class 3: Minimize risk (assess risk and take one or more of the following actions, if needed)

Consider alternatives: alternatives may be available that are less likely to interact

Circumvent: take action to minimize the interaction (without avoiding combination)

Monitor: early detection can minimize the risk of an adverse outcome[30]

Class 4: No special precautions (risk of adverse outcomes appears small)

Class 5: Ignore (evidence suggests the drugs do not interact)[12]

AVOIDANCE OF DRUG INTERACTION

1. Tell your doctor about all the medications you use, including any dietary supplements and health supplements, and any you may have taken recently.

2. Always read the patient information sheet that comes with the medication.[13]

3. Inform your healthcare provider of any lifestyle changes, such as a change in your diet or exercise routine.

4. One pharmacy should be utilised whenever possible for both prescription and non-prescription items. This would be advantageous since the pharmacist could keep track of all your medications and provide advice on drug interactions, side effects, and unpleasant effects starting on day

5. Whenever you believe that someone is taking medication, note the time.

6.The medical professional must be aware of the potential for drug interactions and take the necessary precautions, such as using substitute medications.

7. A prescription decision to start or stop a medicine may result in a drug interaction.

8. Routine care includes checking on patients for drug toxicity or loss of efficacy.

9. Quickly following changes in the prescription, monitoring for changes in symptoms, biomarkers of effect, or drug concentrations enables early identification of drug interactions and minimises harm.[13]

10. Inform the client

CONCLUSION

Drug-drug interactions refers to a common clinical problem during treatment of patients receiving multiple drugs. However, drug interactions between two drugs are clinically relevant to pharmacology of each drug. Understanding of DDIs has greatly improved over the past few years, especially in the area of the molecular mechanisms by which drugs interact. The capacity to effectively apply this knowledge to particular patients, however, has lagged far behind. Pharmacists are in charge of keeping an eye out for drug interactions and alerting doctors and patients to any potential issues.

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