

DRUG

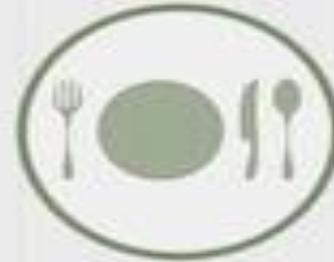
interaction



Drug



Beverage



Food

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INTRODUCTION

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.

Every time a drug is administered with any other prescription medicine, OTC medicine, food item, or herb, we expose ourselves to the risk of a potentially dangerous interactions. The risk of a drug-drug interaction increases with the number of drugs used.

The drug whose activity is effected by such interaction is called as “Object Drug” and the agent which precipitates such an interaction is called as the “Precipitant”.

Drug interactions are thus-

- Mostly undesirable
- Rarely desirable (beneficial) for ex. Enhancement of activity of penicillin when administered with probenecid

Causes Of Drug Interactions

There are many causes of drug interactions. For example, one drug may alter the [pharmacokinetics](#) of another. Alternatively, drug interactions may result from competition for a single [receptor](#) or [signaling pathway](#).

Main factors contributing to drug interactions are-

- Multiple drug therapy
- Multiple prescribers
- Multiple pharmacological effects of drug
- Multiple diseases / illness
- Poor patient compliance
- Advancing age of patient
- Drug related factors

Types Of Drug Interactions

Important types of drug interactions are:

1. Drug-drug interactions
2. Drug -food interactions
3. Drug-chemical interactions
4. Drug-laboratory test interactions
5. Drug-disease interactions

The net effect of a drug- interaction is:

- Generally quantitative – increased or decreased effect.
- Seldom qualitative – rapid or slower effect.
- Precipitation of newer or increased adverse effect.

Mechanisms of Drug Interactions

Behavioral drug-drug interaction: altered compliance

When one drug alters the patients behavior to modify compliance with another drug. For ex. - a depressed patient taking an antidepressant drug may become more compliant to the drug as symptoms improve.

Pharmaceutic drug-drug interactions: outside the body

It is a physicochemical interaction that occurs when drugs are mixed with i.v. infusions causing precipitation or inactivation of active principles before it is administered. For ex.- precipitation of sodium thiopentone within an intravenous dose.

Pharmacokinetic drug-drug interactions : altered concentration or effect

These interactions occur when one drug changes the systemic concentration of another drug, altering how-much or how-long, it is present at the site of action. Pharmacodynamic drug-drug interactions occur when interacting drugs have either additive effects (overall effect increased) or opposing effects (overall effect decreased or even cancelled out).

Pharmacodynamic Interactions

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. 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 different responses of a receptor to the action of a drug has resulted in a number of classifications, such as "partial agonist", "competitive agonist" etc. These concepts have fundamental applications in the [pharmacodynamics](#) of these interactions.

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The change in an organism's response upon administration of a drug is an important factor in [pharmacodynamic](#) interactions. The well-founded suspicion exists that there are more unknown interactions than known ones.

Pharmacodynamic interactions can occur on:

1. 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: a) [Homodynamic](#), if they act on the same receptor. They in turn can be pure agonists, partial agonists or antagonists, and

b) [Heterodynamic](#) competitors, if they act on distinct receptors.

2. 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 [catecholamines](#), which trigger compensation mechanisms thereby increasing blood glucose levels. The release of catecholamines 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).

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3. Antagonistic 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.

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

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](#). 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](#).

Transport and distribution interactions

The main interaction 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.

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Metabolism interactions:

Many drug interactions 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](#)).

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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.

Enzymatic induction

If drug A is metabolized by a cytochrome P450 enzyme and drug B induces or increases the enzyme's activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will take place more rapidly. As a result, enzymatic induction will cause a decrease in the drug's effect.

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 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.

Bile excretion

[Bile](#) excretion 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.

CONCLUSION

It is possible to take advantage of positive drug interactions. However, the negative interactions are usually of more interest because of their pathological significance, 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
- Polypharmacy
- Genetic factors
- Hepatic or renal diseases
- Serious diseases
- Drug dependent factors like Narrow therapeutic index, Steep dose-response curve, Saturable hepatic metabolism.

