



# A PROSPECTIVE STUDY ON DETECTION OF DRUG INTERACTIONS, IMPROVING DRUG SAFETY ACCESS AND THERAPEUTIC OUTCOME IN A TERTIARY CARE TEACHING HOSPITAL

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## I. INTRODUCTION

### 1.1 DRUG INTERACTIONS

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agents.<sup>[1]</sup>

The outcome can be harmful if the interaction causes an increase in the toxicity of the drug.

**Ex 1:** there is a considerable increase in risk of severe muscle damage if patients on statins start taking azole antifungals.

**Ex 2:** patients on warfarin given rifampicin need more warfarin to maintain adequate and protective anticoagulation.

**Ex 3:** while patients taking tetracyclines or quinolones need to avoid antacids and milky fruits because the effects of these antibiotics can be reduced or even abolished if admixture occurs in the gut.

These unwanted and unsought-for interactions are adverse and undesirable but there are other interactions that can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics in order to achieve antihypertensive effects possibly not obtainable with either drug alone.

Sometimes the term drug interaction is used for the physico-chemical reactions that go on if drugs are mixed in intravenous fluids, causing precipitation or in activation. The long-established and less ambiguous term is pharmaceutical incompatibilities.

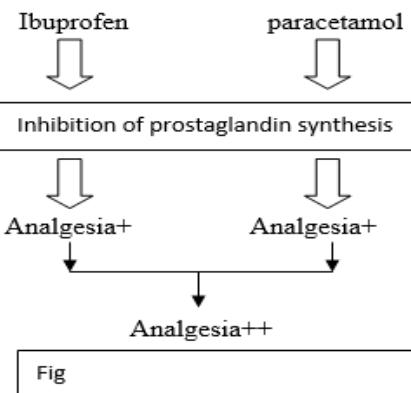
It is therefore easy to see the importance of these pharmacological interactions in the practice of medicine. If a patient is taking two drugs and one of them increases the effect of the other it is possible that an overdose may occur. The interaction of the two drugs may also increase the risk that side effect will occur. On the other hand, if the action of a drug is reduced it may cease to have any therapeutic use because of under dosage. Notwithstanding the above, on occasion these interactions may be sought in order to obtain an improved therapeutic effect (Maria Soledad Fernandez Alfonso, Mariano Ruiz Gayo). Examples of this include the use of codeine with paracetamol to increase its analgesic effect. Or the combination of clavulanic acid with amoxicillin in order to overcome bacterial resistance to the antibiotic. It should also be remembered that there are interactions that, from a theoretical standpoint, may occur but in clinical practice have no important repercussions.

The pharmaceutical interactions that are of special interest to the practice of medicine are primarily those that have negative effects for an organism. The risk that a pharmacological interaction will appear increases as a function of the number of drugs administered to a patient at the same time. [Tannenbaum C, Sheehan NL 2014]. Over a third (36%) of older adults in the U.S regularly use 5 or more medications or supplements and 15% are potentially at risk for a major drug-drug interaction. Both the use of medications and subsequent adverse drug interactions have increased significantly between 2005-2011. [Qato DM, Wilder J et al, 2016]

It is possible that an interaction will occur between a drug and another substances present in an organism (i.e. foods or alcohol). Or in certain specific situations a drug may even react with itself, such as occurs with dehydration. In other situations, the interaction does not involve any effect on the drug. It is possible for interactions to occur outside an organism before administration of the drugs has taken place. This can occur when two drugs are mixed, for example, in a saline solution prior to injection. Some classic examples of this type of interactions include that thiopentone and suxamethonium should not be placed in the same syringe and same is true for benzylpenicilline and heparin.

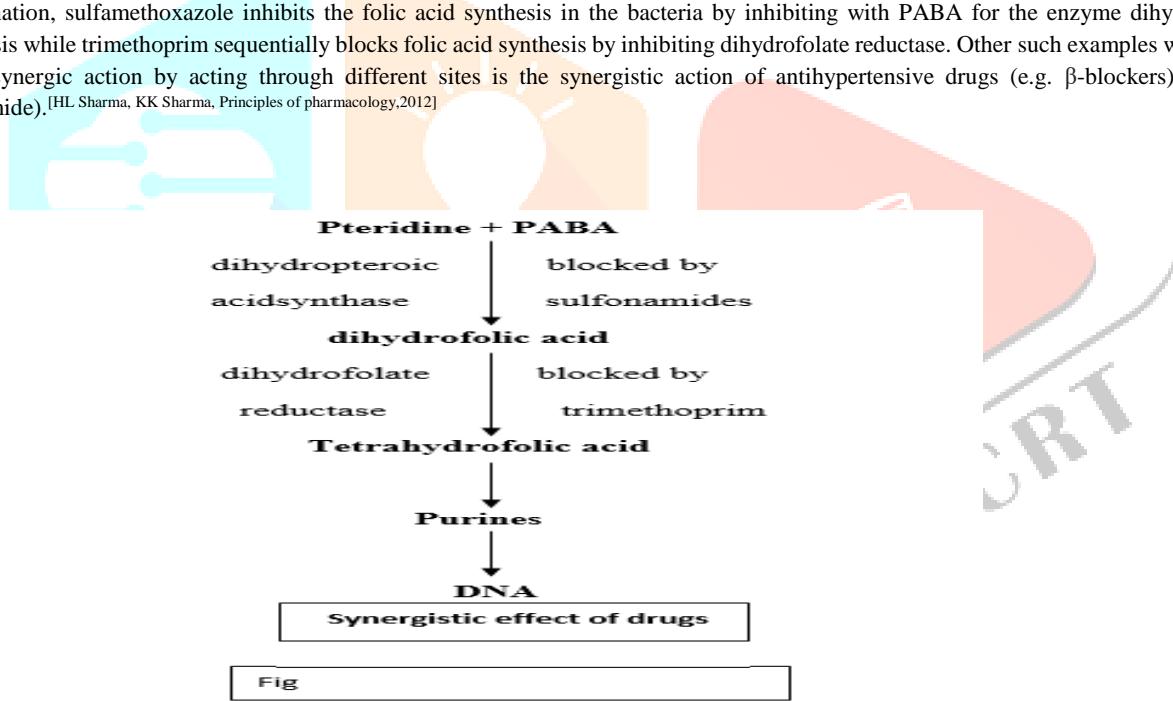
## &lt;div[](img/100px-Additive\_effects.svg) ADDITIVE EFFECTS

1. This term is usually used in those cases in which the combined effect of two drugs, acting by the same mechanism, is equal to that expected by simple addition. For example, ibuprofen and paracetamol apparently act by the same mechanism and hence their combined analgesic effect is an additive effect. [HL Sharma, KK Sharma, Principles of pharmacology, 2012]



## Synergism

When the combined effect of two drugs is greater than the algebraic sum of their individual effects, the phenomenon is called as synergism. The net outcome of synergism is either the potentiation or prolongation of effects. This may result when two drugs act at different sites or when one drug alters the pharmacokinetics of the other drug. The best example of synergistic action of two drugs acting at different sites is that of sulfamethoxazole combined with trimethoprim. Individually, each drug is bacteriostatic but the combination becomes bactericidal. In this combination, sulfamethoxazole inhibits the folic acid synthesis in the bacteria by inhibiting PABA for the enzyme dihydropteroic acid synthesis while trimethoprim sequentially blocks folic acid synthesis by inhibiting dihydrofolate reductase. Other such examples where two drugs show synergic action by acting through different sites is the synergistic action of antihypertensive drugs (e.g.  $\beta$ -blockers) with diuretics (frusemide). [HL Sharma, KK Sharma, Principles of pharmacology, 2012]



**Table no 1.1: Examples of drug interactions.**

Drugs	Result of interaction
Antihypertensives + drugs causing hypotension (Phenothiazines, Sildenafil)	Increased anti hypertensive effects; orthostasis
Beta-agonist bronchodilators + potassium-depleting drugs	Hypokalaemia
Drugs that prolong the QT interval + other drugs that prolong the QT interval Amiodarone + Disopyramide	Additive prolongation of QT interval, increased risk of torsade de pointes
Methotrexate + Antibacterials; Co-trimoxazole	Bone marrow megaloblastosis due to folic acid antagonism

## Drug antagonism

Anytime when the combined effect of two drugs is less than the sum of the individual drugs, the phenomenon is called as drug antagonism. There are four mechanisms by which one drug may oppose the action of another, and these are:

### Chemical antagonism:

This is when the drugs act merely as chemical antidotes to each other; for instance, the anticoagulant effect of the strong negatively charged macromolecule heparin is antagonized by protamine which is a highly positively charged protein. This is analogous to the neutralization of excess gastric acid by any of the antacids like aluminum hydroxide, magnesium hydroxide or sodium bicarbonate; or to the chelating actions of drugs, like BAL or calcium sodium edentate, which form inactive soluble complexes with heavy metals like arsenic or lead. [HL Sharma, KK Sharma, Principles of pharmacology, 2012]

## 2) Physiological or functional antagonism

This is when two agonists, acting at different receptors, counterbalance each other by producing opposite effects on the same physiological system. For example, CNS stimulants antagonize the effects of CNS depressants, or the effects of histamine on blood pressure (vasodilation) can be cancelled out by norepinephrine (vasoconstriction). The essential point about physiological antagonism is that the effects produced by the two drugs counteract each other, but each drug is unhindered in its ability to elicit its own response (unlike pharmacological antagonism)

## 3) Pharmacological antagonism

It is a pharmacodynamic antagonism wherein the antagonist either competes with the agonist for its binding sites on the receptor (competitive antagonism) or may antagonize the effects of agonist by acting at a site different from the agonist receptor site (non-competitive antagonism)

### a) Competitive antagonism

This is the most commonly observed pharmacological antagonism. Here, the antagonist combines and competes with the same receptor site as does the agonist but does not induce its own response (i.e., has no intrinsic effect). These are classified into three subtypes depending on the type of the bonding formed between the agonist and the receptor.

#### i) Reversibly Competitive or Equilibrium competitive Antagonism:

This type of antagonism is frequently observed with antagonists that bind reversibly (by forming weak bonds) to the same receptor sites as that of the agonists. Hence the antagonism can be overcome, and the maximal response of the antagonist can be attained if the concentration of the agonist, in the bio-phase is increased. Conversely, if the dose of the antagonists is increased the amount of agonist required to produce the maximal response would be greater, i.e., ED<sub>50</sub> of the agonist in the presence of a competitive antagonist increases. The log dose-response curves of the agonist, in the presence of increasing doses of antagonist would show a parallel shift towards right because the agonist now is acting simply as less potent and all its doses towards right will be equally spaced and parallel. The duration of the reversible competitive blockade is short due to higher rate of dissociation of antagonist from the receptor sites. As a result, the addition of higher concentration of agonist reduces the overall receptor occupancy of the antagonist and a competitive equilibrium is rapidly established between the agonist and the antagonist.

Examples: atropine is a reversibly competitive antagonist of acetylcholine or bethanechol at various muscarinic receptors, naloxone is a similar antagonist of morphine at different opioid receptors while propranolol is a similar antagonist of norepinephrine at beta-1 adrenoceptor.

#### ii) Irreversibly competitive or Non-Equilibrium Competitive Antagonism:

Such antagonists also have only the affinity for the same receptor sites (as of the agonists) but bind to it in an irreversible manner by forming a stable covalent bond. Here the antagonists dissociate very slowly or not at all from the receptors and its effects cannot be overcome even by increasing the concentration of the agonist. Characteristically, the LDR curves of the agonist (in presence of this antagonist) would show reduced efficacy (i.e., reduced maximal response of the agonist) but unaltered potency (i.e., no change in the location of the curve at dose axis). The duration of action of the irreversible antagonist is no longer as its rate of dissociation from the receptor is very slow. As a result an equilibrium between the antagonist and the agonist cannot be established even after increasing the doses of agonist (hence the term 'non-equilibrium competitive antagonism').

Example:Dibenamine(a haloalkylamine) is an irreversible competitive antagonist of norepinephrine at alpha-1adrenoceptor.

#### iii) Pseudo-reversible Antagonism:

1. In few cases the classical irreversible antagonism, may not be that obvious. This happens due to a lesser degree of receptor occupancy by pseudo reversible type of antagonist, and also due to availability of spare receptors. As a result, increasing concentrations of the agonists, in presence of such antagonist will initially shift the LDR curves to the right showing the maximal response (because of the response from spare receptors), but eventually if the concentration of this antagonist is increased there will be reduction in the maximal response. Hence the term 'pseudo-reversible competitive antagonism'. [HL Sharma, KK Sharma, Principles of pharmacology,2012]

### b) Non-Competitive Antagonism:

Some texts refer the "irreversible antagonism" as "non-competitive antagonism". It is now clear that the term "non-competitive" should be reserved for antagonism that does not involve occupation of same receptor sites. It is of two types: the antagonist may interfere with the down-stream events after receptor activation by the agonist or a drug may antagonize the effects of other drug by acting at a modulator site of the receptor beyond the binding site for the agonist.

i) Non-Competitive Antagonism Through Interference in the Down-Stream Events of Receptor Activation: as noticed, that two agonist-nor epinephrine and angiotensinII – interact with totally different receptors- alpha-1 adrenoceptor and AT<sub>1</sub> receptor, respectively- to initiate a chain of events (free Ca<sup>2+</sup> entry and depolarization) leading to vasoconstriction. These receptors also have their own competitive antagonist like prazosin (an alpha-1 adrenoceptor antagonist) and losartan (an AT<sub>1</sub> receptor antagonist). Drugs like verapamil or nifedipine (Ca<sup>2+</sup> channel blockers) are not providing antihypertensive effects by virtue of being alpha-1 or AT<sub>1</sub> receptor antagonist by preventing the opening of voltage-gated Ca<sup>2+</sup> channels. Thus, they inhibit the Ca<sup>2+</sup> entry associated with depolarization which leads to vasodilatation. Calcium channel blocking drugs are therefore non-competitive antagonist of both nor epinephrine and angiotensin II because instead of blocking alpha-1 or AT<sub>1</sub> receptors, they have blocked the down-stream chain of events due to receptor activation by both these agonists. The non-competitive antagonism, as well as the irreversible competitive antagonism exhibit the same pattern of LDR curve, but the irreversible competitive antagonists is specific against one type of agonists, while the non-competitive antagonists are non-specific in action as they can antagonize different agonists acting through more than one receptor system, provided where final down-stream events are same.

#### ii) Antagonism Through Allosteric Receptor Site Binding:

Allosteric receptor antagonists bind to the receptor at a site other than the agonist site. They do not compete directly with agonist for receptor binding but rather prevent the receptor activation by the agonist. Example: flumazenil (by binding to benzodiazepine site) antagonizes the effects of benzodiazepines by preventing the binding of GABA to GABA<sub>A</sub> receptor. Hence flumazenil does not compete directly with the agonist (GABA) for its binding site at GABA<sub>A</sub> receptor but rather prevents its activation by modulation through allosteric binding. Such antagonist's don't affect the inherent basal receptor activity (as of GABA<sub>A</sub> receptor, of inverse agonists).

- Similarly, bicuculline which is a competitive antagonist of binding of GABA to its receptor sites, indirectly blocks the effects of benzodiazepines like diazepam non-competitively, because benzodiazepines facilitate GABAergic activity by binding at the modulatory site of GABA receptor (i.e., binding sites of both the drugs are different). [HL Sharma, KK Sharma, Principles of pharmacology,2012]

Drug interactions may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion (ADME) of drug. Alternatively, drug interactions may be the result of the pharmacodynamic properties of the drug, e.g. the co-administration of a receptor antagonist and an agonist for the same receptor. Drug interactions can be divided into pharmacodynamics interactions and pharmacokinetic interactions.

**Table no-1.2: examples of drugs that shows antagonism effect.**

Drugs affected	Interacting drugs	Results of interaction
ACE inhibitors or loop diuretics	NSAIDs	Anti hypotensive effects opposed
Anticoagulants	Vit - k	Anticoagulant effects opposed
Anti diabetics	Glucocorticoids	Hypoglycemic effects opposed
Anti neoplastics	Megestrol	Cytotoxic effects possibly opposed
Levodopa	Tacrin	Anti parkinsonian effects opposed
Levodopa	Anti psychotics (those with dopamine antagonist effects)	Anti parkinsonian effects opposed

**Pharmacokinetic interactions:**

Pharmacokinetic interactions may change the exposure to the drug causing increasing the effect, adverse effect or absence of effect. Pharmacokinetic interactions may involve absorption, distribution, transport, metabolism, excretion (renal or fecal) of the drug.

Absorption interaction can occurs when e.g. the drug bind to cations. For example when doxycycline is co-administered with magnesium ions, doxycycline binds to the magnesium forming a salt that cannot be absorbed the uptake of doxycycline is decreased significantly and the combination may lead lack of antibiotic effect. Absorption interaction can also be due to alteration in gastric pH. One example is the HIV protease inhibitor. Atazanavir, which needs a low pH to be sufficiently absorbed. If a proton pump inhibitor is given the exposure to atazanavir is decreases by 62-95% and this may result in reduced antiviral activity.

Distribution interactions occur mainly due to competitive binding to plasma proteins. This interaction may occur when two drugs that are highly bound to the same plasma protein are co-administered. This type of interaction gives an increase in free fraction of the drugs, which may cause adverse effect if they have narrow therapeutic intervals. One example of such drug is phenytoin and interactions with acetylsalicylic acid, and valproic acid have been reported. These interactions often lack clinical significance since they usually are transient.

Interactions involving transport can increase or decrease the effect of drugs. An example of a drug interaction at transporter level is the interaction between digoxin and verapamil, where inhibition of P-gp by verapamil increases the plasma concentration of digoxin. Another example is the interaction between cyclosporine and atorvastatin, where cyclosporine inhibits the transport of atorvastatin by OATP1B1. This result in decreased uptake of atorvastatin into liver cells, and thereby decreased metabolism and increased statin concentrations.

Metabolic interactions are usually caused by either inhibition or induction of a metabolic pathway. CYP mediated interactions have been well studied and much knowledge is available. One of the most pronounced CYP interactions is between lopinavir/ritonavir and tacrolimus, where the tacrolimus dose may have to be reduced by 99% due to inhibition of CYP3A4. Induction of CYP enzymes can also cause dramatically decreased drug concentration. For example, rifampicin reduces the bioavailability of nifedipine by 88% and decreases S-warfarin exposure by 75%.

Interactions can also occur due to inhibition or induction of UGTs. Valproic acid is a known inhibitor of several UGT enzymes, and clinically relevant interactions occur with UGT substrates such as Lamotrigine and mycophenolic acid. Induction interactions have been reported between Lamotrigine and inducers such as rifampicin and carbamazepine. Much unknown regarding drug interactions caused by inhibition or induction of UGTs.

Drug interactions involving urinary excretion can occur when for example one drug changes the pH of urine causing less excretion of other drug. Changes in renal blood flow can also change the excretion of drugs. NSAIDs can decrease renal blood flow and this may cause increased concentration of lithium, which is excreted in unchanged form in urine.

- 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 concentrations of the drugs. In the respect two drugs can be homeric if they have the same effect in the organism and the heteric if their effects are different.

**Absorption interactions****Changes in motility**

Some drugs, such as the prokinetic agents increases the speed with which a substance passes through the intestines. If a drug is present in the digestive tracts 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 ionized or non-ionized form, depending on their pKa (pH at which the drug reaches equilibrium between its ionized and non-ionized form). [Malgor- Vlascia, 2008] The non-ionized forms of drugs are usually easier to absorb, because they will not be repelled by the lipidic by-layer 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 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 drugs state between ionized or not, can be useful or not 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 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. [Alicia Gutierrez Valanvia y Luis F, 2008]

- 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.
- From chelation 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 external feeding. [MardagaSanz, Mariano]
- 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 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.<sup>[Tattro, DS,2004]</sup>

**Table no-1.3: some drug absorption interactions.**

Drug affected	Interacting drugs	Effect of interaction
• Digoxin	• Metoclopramide • Propantheline	• Reduced digoxin absorption • Increased digoxin absorption (due to changes in gut motility).
• Digoxin • Levothyroxine • Warfarin	• Cholestyramine	• Reduced absorption due to binding/ complexation with cholestyramine
• Ketoconazole	• Antacids • H <sub>2</sub> -blockers • PPI	• Reduced ketoconazole absorption due to reduced dissolution
• Methotrexate	• Neomycin	• Neomycin-induced malabsorption state.

### 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 mechanism 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 an account if there other associated problems are present such as when the method of excretion is affected.[Valsecia, Mabel en]

### 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.<sup>[Elizabeth Lipp, 2008]</sup> One notable system involved in metabolic drug interactions is the enzyme system comprising the Cytochrome p450 oxidases.

#### CYP450

Cyt450 is very large family of hemoproteins that are characterized by their enzymatic activity and their role in the metabolism of a large number of drugs.<sup>[Danielson PB,2002]</sup> 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, CYP2C9, CYP2D6, CYP2E1, CYP3A4.<sup>[25]</sup> 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).

#### 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 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<sub>2</sub>, which actually produces the effect of the drug. If the metabolism of drug A is inhibited by drug B the concentration of A<sub>2</sub> that is present in the blood will decrease, as will the final effect of the drug.

#### ENZYMATIC INDUCTION

If drug A is metabolized by a Cytochrome p450 enzyme and drug B induces or increases the enzyme activity, the 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. As in the previous case it is possible to find paradoxical situations where an active metabolite causes the drug's effect. In this case the increase in active metabolite A<sub>2</sub> (following the previous example) produces an increase in the drug's effect.

It can often occur that a patient is taking two drugs that are enzymatic inducers. One inductor and the other inhibitor or both inhibitors, which greatly complicates the control of an individual's medication and the possible adverse reactions.

An example of this is shown in the following table for the CYP1A2 enzyme, which is the most common enzyme found in the human liver. The table shows the substrates (drugs metabolized by this enzyme) and the inducers and inhibitors of its activity.<sup>[Nelson D, 2003]</sup>

**Table no-1.4.1: Examples of enzyme induction interactions related to CYP1A2.**

Drugs related to CYP1A2	Inhibitors	inductors
• Caffeine • Theophylline • Phenacetin • Clomipramine • Clozapine • thioridazine	• omeprazole • nicotine • cimetidine • ciprofloxacin	• phenobarbital • fluvoxamine • venlafaxamine • ticlopidine

Enzyme CYP3A4 is the enzyme that the greatest number of drugs use as a substrate. Over 100 drugs depend on its metabolism for their activity and many others act on the enzyme as inducers or inhibitors.

**Table no-1.4.2: Examples of enzyme induction interactions related to CYP3A4.**

Some foods also act as inducers or inhibitors of enzymatic activity. The following table shows the most common: Ephedra	Receptor level agonist	MAOI, central nervous system stimulants, alkaloids ergotamines and xanthines.
Kava (Piper methysticum)	Unknown	Levodopa
Ginger	Inhibits thromboxane synthetase (in vitro)	Anticoagulants
Chamomile	Unknown	Benzodiazepines, barbiturates and opioids
Hawthorn	Unknown	Beta-adrenergic antagonists, cisapride, digoxin, quinidine

Any study of pharmacological interactions between particular medicines should also discuss the likely interactions of some medicinal plants. The effects caused by medicinal plants should be considered in the same way as those medicines as their interaction with organism gives rise to pharmacological response. Other drugs can modify this response and also the plants can give rise to a pharmacological response. Other drugs can modify this response and also the plants can give rise to changes in the effects of other active ingredients. There is little data available regarding interactions involving medicinal plants for the following reasons:

1. **False sense of security** regarding medicinal plants. The interaction between a medicinal plant and a drug is usually overlooked due to a belief in the "safety of medicinal plants."
2. **Variability of composition**, both quality and quantity. The composition of a plant-based drug is often subject to wide variations due to a number of factors such as seasonal differences in concentrations, soil type, climatic changes or the existence of different varieties or chemical races within the same plant species that have variable compositions of the active ingredient. On occasion an interaction can be due to just one active ingredient, but this can be absent in some chemical varieties or it can be present in low concentrations, which will not cause an interaction. Counter interaction can even occur. This occurs, for instance, with ginseng, the panaxginseing variety increases the prothrombin time, while the Panaxquinquefolius variety decreases it. [Zaragoza F, Ladero M, Rabasco AM et al, 2012]
3. **Absence of use in at-risk groups**, such as hospitalized and poly pharmacy patients, who tend to have the majority of drug interactions.
4. **Limited consumption** of medicinal plants has given rise to a lack of interest in this area. [Zaragoza F, Ladero M, Rabasco AM et al, 2001]

They are usually included in the category of foods as they are usually taken as a tea or food supplement. However, medicinal plants are increasingly being taken in a manner more often associated with conventional medicines: pills, tablets, capsules, etc.

### 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. [Gago-Banderas, F] Creatine clearance is used as a measure of kidney functioning but it is only useful in the cases where the drug is excreted in an unaltered form in the urine. The excretion of drugs from the kidneys 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 pH of the urine, it having been shown that the drugs that acts 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 is different from kidney excretion as it is 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 drug 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 entero-hepatic circuit), which can also lead to interactions with other drugs.

### PHARMACODYNAMICS INTERACTIONS

Pharmacodynamics interactions occur when the effect of a drug is altered due to another drug without any alterations in pharmacokinetics. Interactions can be additive when e.g. two drugs are can be agonist of the same receptor, and concomitant use causes an increased effect and also an increased risk of adverse effect one example of an additive pharmacodynamics interactions is concomitant use of MAO-inhibitors and serotonin reuptake inhibitors (SSRIs). SSRIs blocks the reuptake of serotonin in synapsis and monoamine oxidase degrades serotonin in the synapses. When both the uptake and degradation of serotonin is inhibited. The synaptic concentration of serotonin increases dramatically and this causes over stimulation of serotonin receptors. The clinical symptoms of serotonin syndrome tremors myclonas, confusion and agitation. In worst case, serotonin syndrome may cause hyperthermia and muscle rigidity which may be fatal. Other combinations of serotonergic drugs may also cause serotonin syndrome.

Another example of pharmacodynamics interactions is the one between SSRIs and non-steroidal anti-inflammatory drugs (NSAIDs). Both drug classes increase the risk for gastric intestinal hemorrhages and the risk is increased up to six fold when they are co-administered. Classical agonist-antagonist interactions are also classified as pharmacodynamics interactions. One example is effect of beta stimulant for asthma treatment in patient using unselective beta blockers. Another example is reduced effect of Warfarin. When patient treated with Warfarin ingest large amount of vitamin-K.

The change in an organism's response on administration of a drug is an important factor in pharmacodynamic interactions'. These changes are extraordinarily difficult to classify given the wide variety of modes of action exist and the fact that many drugs can cause their effect through a number of different mechanisms. This wide diversity also means that, in all but the most obvious cases, it is important to investigate and understand

these mechanisms. The well-founded suspicion exists that there are more unknown interactions than known ones. Pharmacodynamic interactions can occur on:

**Pharmacological receptors:** <sup>[15]</sup> 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:

- 1) Pure agonists, if they bind to the main locus of the receptor, causing a similar effect to that of the main drug.
- 2) Partial agonists if, on binding to one of the receptors secondary loci, they have the same effect as the main drug, but with a lower intensity.
- 3) Antagonists, if they bind directly to the receptors main locus but their effect is opposite to that of the main drug. These include

I) 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.

II) Uncompetitive antagonist, when the antagonist bind to the receptor irreversibly and is not released until the receptor is saturated. In principle the quantity of 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.

**B) 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<sup>[S Gonzalez, 2009]</sup>.

For example, it is known that hypoglycemia (low blood glucose) in an organism produces a release of catecholamine, which triggers compensation mechanisms thereby increasing the blood glucose levels. The release of catecholamine also triggers a series of symptoms, which allows the organism to recognize 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 adrenalin receptors. This will block the reaction triggered by the catecholamine's should a hypoglycemic episode occur. Therefore, the body will not adopt corrective mechanisms and there will be an increased risk of serious reaction resulting from the ingestion both drugs at the same time.

**Antagonistic physiological systems:** <sup>[17]</sup> imagine 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 directly increased by the action of the drug **B**. An actual example of this interaction is found to be in the concomitant use of digoxin and furosemide. The former acts on the cardiac fibers and its effect is increased if there are low levels of potassium (K) in the blood plasma. Furosemide is a diuretic that lowers arterial tension but favours the loss of K<sup>+</sup>. This could lead to hypokalemia (low levels of potassium in the blood), which could increase the toxicity of digoxin.

## DRUG INTERACTIONS-OCCURRENCE AND CLINICAL RELEVANCE

### Evaluation of drug interaction studies

Drug interactions can be studied in many ways. In vitro system using human liver microsomes give information about which enzymes that may be involved in the metabolism of a drug. Results from in vitro studies should be used as an indication of interaction but not as evidence of an interaction.

Many drug interaction studies are performed as cross-over studies in healthy volunteers. Results from these studies give valuable information about drug interactions in general. There are, however, some limitations to this kind of studies. The number of study subjects is usually small, and inclusion of a single patient with different genotype or some other reason for altered pharmacokinetics may influence the result. It is also important that the doses used are the same as therapeutic doses, since pharmacokinetics may be different using other doses. The length of drug administration may also be important and steady-state data is often aimed for. If induction is studied the length should, ideally, be long enough to reach maximum induction and a new steady-state.

Drug interactions may be studied using data from TDM databases. Interactions are studied by comparing concentrations/dose ratios among exposed versus unexposed patients. When evaluating these studies one should bear in mind that patient data in a TDM material may not be representative for all patients since TDM is often used when a problem occurs. However, using TDM data may also have benefits since the measurements are made in patients and not in healthy volunteers, thus it could be more representative for the users of the drugs.

### Prevalence of drug interactions

Drug use has increased steadily since more drugs have entered the market and also because the population tends to get older and older. Between 2005 and 2008, the total drug use (defined as number of drugs during 3 months) per patient in Sweden increased by 3.6% and the total prevalence of polypharmacy (patients with five or more drugs) increased by 8.2%. The number of patients exposed to 10 or more drugs increased by 15.7% [148]. Another, older Swedish study revealed that the number of drugs used by patients 77 years or older had increased from 2.5 to 4.4 between 1992 and 2002, while the prevalence of polypharmacy in this age group increased 3-fold (from 18 to 42%). [Haider SI, Johnell K, et al, 2007.]

The risk for drug interactions increases dramatically by the use of more drugs. Theoretically, the maximal number of potential drug-drug interactions in an individual patient can be described by this formula:

$$\frac{\text{Number of drugs}^2 - \text{number of drugs}}{2}$$

For example a patient using three drugs may in worst case be exposed to three interactions. A patient using five drugs may have ten interactions, and a patient using ten drugs may, at least theoretically, be exposed to 45 drug interactions. Increase in polypharmacy may therefore greatly increase the prevalence of drug-drug interactions. Of course, it is almost impossible that every drug used by a patient on 10 drugs would interact with every other drug but it shows that the potential for interactions in the emergency department, the risk of a potential drug interaction was 13% among users of two drugs and it was as high as 82% among patients using seven or more drugs. In another study investigating CYP mediated drug interactions among patients on polypharmacy the probability of at least one drug interaction was calculated. The risk was 50% in patients using 5-9 drugs, 81% in those using 10-14 drugs, 92% in those with 15-19 drugs and 100% in patients using more than 20 drugs. [Doan J, Zakrzewski-Jakubiaik H, et al, 2013.] In a Dutch study the prevalence of drug interactions in patients aged 70 or older was increased from 10.5% to 19.2% between the years 1992 and 2005. The prevalence of serious drug interactions (potentially life threatening) almost doubled from 1.5% to 2.9%. [Becker ML, Visser LE, et al, 2008.]

Many studies have investigated the prevalence of potential drug interactions based on prescription data and figures ranging from 6 to 89% have been reported. [Magro L, Moretti U, et al, 2012]. Data from these kind of studies are almost impossible to compare since the definition of potential drug-drug interactions often are differently classified, and a DDI classified as severe in one database might be classified as of minor importance in another database or is completely missing. The source has great influence on the number of interactions found since some drug interaction databases only include a small number of drug-drug interactions while others may include many more e.g. Swedish Finnish Interaction X-referencing (SFINX) can today identify more than 17,000 drug-drug interactions. In a yet unpublished study based on all dispensed drugs in Sweden during 4 months, the total number of interacting drug combinations according to SFINX were >2,000,000. The prevalence of C and D interactions were (n > 900,000), and (n = >90,000) respectively. [Johan Holm, 2014] In the end of 2013 there were around 9.6 million people living in Sweden. [SCB, 2014] Of more interest are studies investigating actual drug-drug interactions that have caused some kind of clinical problem and lead to hospitalization or emergency department visits. In a large review of published studies the overall incidence of drug-drug interactions resulting in emergency department visit was 0.054%, and 0.57% for hospitalizations. However, in elderly patients drug-drug interactions were assumed to be the cause of 4.8% of admissions. [Becker ML, Kallewaard M, et al, 2007.] In general the risk of adverse drug interactions leading to hospital admission seems to be low

but several studies suggest that it is much more common in elderly patients than in younger. This is in line with the increased number of drugs used by the elderly. They may also be more prone to drug interactions due to for example decreased renal function exposing them to higher drug concentrations. In some patient groups such as HIV- patients, patients using anti-convulsants and patients on chemotherapy the risk for hospitalization is probably higher due to use of interacting drugs with narrow therapeutic intervals.

#### Drug interactions with food or natural remedies

Some drugs may interact with food. Calcium containing products such as milk and yoghurt may, by chelate formation, decrease the uptake of tetracyclines and fluoroquinolones. The uptake of ciprofloxacin may be lowered by approximately 30-40% which may result in therapeutic failure. Grapefruit juice has been shown to be a potent inhibitor of CYP3A4 and P-gp and ingestion may cause dramatic increases in the concentration of drugs that have low bioavailability such as nifedipine the interaction is mostly due to inhibition of intestinal CYP3A4 and P-gp. Other fruit juices may also influence the pharmacokinetics of drugs. The active constituent of grapefruit juice is uncertain. Grapefruit contains naringin, which degrades during processing to naringenin, a substance known to inhibit CYP3A4. Because of this, it has been assumed that whole grapefruit will not interact, but that processed grapefruit juice will. However, subsequently some reports have implicated the whole fruit. Other possible active constituents in the whole fruit include bergamottin and dihydroxybergamottin. (Ref) 11 -stockley's.

Orange juice can decrease bioavailability of atenolol and pomegranate juice has in a few cases been shown to increase the effect of Warfarin. (Natural remedies can also cause clinically important drug interactions. St John's wort is a potent inducer of CYPs concomitant use may cause pronouncedly decreases concentrations of other drugs. Many pregnancies have been reported due to lack of effect of oral contraceptives. Other herbs such as gingko biloba, and ginseng also interact with drugs.)

Smoking is a life style factor that may have great influence on drug therapy. Smoking induces CYP1A2 and e.g. clozapine exposure is about 40% lower in smoking patients.

#### DIETARY SUPPLEMENTS & HERBAL MEDICATIONS

The medical use of plants in their natural and unprocessed form undoubtedly began when the first intelligent animals noticed that certain food plants altered particular body functions. While there is a great deal of historical information about the use of plant-based supplements, there is also much unreliable information from poorly designed clinical studies that do not account for randomization errors, confounders, and-most importantly—a placebo effect that can contribute 30-50% of the observed response. Since the literature surrounding dietary supplements is evolving, reputable evidence-based resources should be used to evaluate claims and guide treatment decisions. An unbiased and regularly updated compendium of basic and clinical reports regarding botanicals is Pharmacists Letter/Prescribers Letter Natural Medicines Comprehensive Database. Another evidence based resources is Natural Standard, which includes an international, multi-disciplinary collaborative website, <http://www.naturalstandard.com>.

For legal purposes, "dietary supplements" are distinguished from "prescription drugs" derived from plants (morphine, digitalis, atropine, etc.) by virtue of being available without a prescription and, unlike "over-the-counter," medicines are legally considered dietary supplements rather than drugs. This distinction eliminates the proof of efficacy and safety priority to marketing and also places the burden of proof on the FDA to prove that a supplement is harmful before its use can be restricted or removed from the market. Furthermore, marketed dietary supplements are not tested for dose response relationships or toxicity and there is a lack of adequate testing for mutagenicity, carcinogenicity, and teratogenicity. Although manufacturers are prohibited from marketing unsafe or ineffective products, the FDA has made significant challenges from the supplement industry largely due to the strong lobbying effort by supplement manufacturers and the variability in the interpretation of the dietary supplements Health and Education Act (DSHEA). The DSHEA defines dietary supplements as vitamins, minerals, herbs or other botanical, amino acids or dietary supplements used to supplement the diet by increasing dietary intake, or concentrates, metabolites, constituents, extracts, or any combination of these ingredients.

#### DRUG-HERB INTERACTIONS:

The market for herbal medicines and supplements in the Western world has markedly increased in recent years and not surprisingly, reports of interactions with 'conventional' drugs have arisen. [Miller LG, 1998.] There have also been isolated reports of other herbal drug interactions, attributable to various mechanisms, including additive pharmacological effects. [Fugh-Berman A, 2000]

To aid collection of data in this area, health professionals should routinely ask patients about their use of herbal medicines and supplements, and report any unexpected responses to treatment.

An additional problem in interpreting these interactions, is that the interacting constituent of the herb is usually not known and is therefore not standardized for. It could vary widely between different products, and batches of the same product.

#### Example:

The most well-known example is the interaction of St John's wort (*Hypericum perforatum*) with a variety of drugs. Evidence has shown that the herb can induce the cytochrome P450 isoenzyme CYP 3A4, and can also induce 'P-glycoprotein'. Hence St John's wort decreases the levels of 'cyclosporine' and 'digoxin' respectively. Other less certain evidence suggests that CYP2E1 and CYP1A2 may also be induced. [Wang Z, Gorski JC et al, 2001.] St John's wort has serotonergic properties, and this has resulted in a pharmacodynamic interaction with the 'SSRIs', namely the development of the serotonin syndrome. [Henderson L, Yue QY et al, 2002.] St John's wort contains many possible constituents that could be responsible for its pharmacological effects. The major active constituents are currently considered to be hyperforin (a phloroglucinol) and hypericin (a naphthodianthrone). Hyperforin is the only constituent that is standardized for and then only in some St John's wort preparations. [Dresser GK, Schwarz UI et al, 2003.]

#### References for drug-herb:

#### CLINICAL ASPECTS OF THE USE OF BOTANICALS

Many U.S. consumers have embraced the use of dietary supplements as a "nature" approach to their health care. Unfortunately, misconceptions regarding safety and efficacy of the agents are common, and the fact that a substance can be called "natural" does not of course guarantee its safety. In fact, botanicals may be inherently inert or toxic. If a manufacturer does not follow GMP this can also result in intentional or unintentional plant species substitutions (e.g., misidentification), adulteration with pharmaceuticals, or contamination.

Adverse effects have been documented for a variety of dietary supplements, however, under-reporting of adverse effects is likely since consumers don't routinely report, and don't know how to report an adverse effect if they suspect that the event was caused by consumption of a supplement. Furthermore, chemical analysis is rarely performed on the products involved, including those products that are described in the literature as being linked to an adverse event. This leads to confusion about whether the primary ingredient or an adulterant caused the adverse effect. In some cases, the chemical constituents of the herb can clearly lead to toxicity.

An important risk factor in the use of dietary supplements is the lack of adequate testing for drug interactions. Since botanicals may contain hundreds of active and inactive ingredients, it is very difficult and costly to study potential drug interactions when they are combined with other medications. This may present significant risk to patients.

**Table no-1.5: various supplements and associated risks.**

Commercial name, scientific name, plant parts.	Intended use	Toxic agents, effects	Comments
<ul style="list-style-type: none"> <li>aconite aconitum species</li> <li>black cohosh cimicifugaracemosa</li> <li>chaparral larrea tridentate twigs, leafs</li> <li>ephedra, Ma-huang ephedra species</li> <li>gland-derive extracts(thymus, adrenal, thyroid)</li> <li>kava-kava</li> <li>pokeroot phytolakka Americana</li> <li>royal jelly of ephismellifera</li> </ul>	<ul style="list-style-type: none"> <li>analgesic</li> <li>menopausal symptoms</li> <li>anti-infective;anti-oxidant;anti-cancer</li> <li>diet aid-stimulant – bronchodilator</li> <li>hormone replacement</li> <li>anxiety</li> <li>anti-rheumatic</li> <li>toxic</li> </ul>	<ul style="list-style-type: none"> <li>alkaloid, cardiac and cns effects</li> <li>hepatotoxicity</li> <li>hepatotoxicity</li> <li>cns toxicity, cardiac toxicity</li> <li>risk of bacterial, viral, or prion transmission</li> <li>hepatotoxicity</li> <li>haemoragic gastritis</li> <li>bronchospasm, anaphylaxis</li> </ul>	<ul style="list-style-type: none"> <li>avoid</li> <li>avoid</li> <li>avoid</li> <li>avoid in-patients at risk, MI, HTN.</li> <li>Avoid</li> <li>Avoid</li> <li>Avoid</li> <li>Avoid in-patients with allergies.</li> </ul>

### 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 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 or favor the appearance of interactions include: [9]

- Old age: factors relating to how many physiological 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 the increases the chances of errors being made in the administration of drugs.[10]
- Poly pharmacy: the more drugs a patient takes the more likely it will be that some of them will interact [11]

### Polypharmacy and interactions

- The more drugs a patient uses the more likely is the risk of being exposed to drug-drug interactions. When concomitant drugs interacting in several ways are co-administered the net result of an interaction is difficult to assess and it can also differ among patients due to environmental and genetic factors.
- For many drugs , metabolism may be dependent on more than one CYP, and if one of the CYPs is inhibited no clinically relevant interaction may be observed, but if the other path also is inhibited the patient might be exposed to a significant interaction . for example, oxycodone is metabolized by both CYP3A4 and CYP2D6. Inhibition of one of the enzymes does not cause a clinically significant change in the effect but inhibition of both enzymes may cause dramatically increased concentration [146], which may cause respiratory depression. Such a case could easily occur for example in a patient treated with fluoxetine, inhibiting CYP2D6 [57], for depression and started on erythromycin, inhibiting CYP3A4 [75], for treatment of a respiratory infection.
- 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 isozymes of cyp 450

### Pharmacogenetic differences

- Pharmacogenetics may also influence the occurrence of drug interactions. In the case of oxycodone the drug effect is not significantly altered in poor metaboliser of CYP2D6 but if a CYP3A4 inhibitor is co-administered the concentration will increase dramatically[146].
- If an inhibitor of CYP2D6 is given to a poor metaboliser, the concentration of a CYP2D6 substrate will not be altered [147], since the patient does not have any CYP2D6 that can be inhibited.The same is true for CYP2C19 and one such example is the interaction between diazepam and omeprazole. Omeprazole increases the concentration of diazepam in extensive metaboliser of CYP2C19 whereas o significant change is observed in poor metabolisers[51].

- Hepatic or renal diseases: any damage to these systems there is the more chance of occurring drug interactions.
- Serious diseases that could worsen if the dose of the medicine is reduced.
- Drug-dependent factors<sup>[12]</sup>
  - 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 concentrations in the patient's blood plasma.
  - Saturable hepatic metabolism: in addition to dose effects the capacity to metabolize the drug is greatly decreased

In certain cases, the presence of a drug in an individual's blood may affect certain types of laboratory analysis (analytical interference).

#### Analytical interference:

The detection of laboratory parameters is based on physicochemical reactions between the substance being measured and reagents designed for this purpose. These reactions can be altered by the presence of drugs giving rise to an overestimation or an underestimation of the real results. Levels of cholesterol and other blood lipids can be overestimated as a consequence of the presence in the blood of some psychotropic drugs. These overestimates should not be confused with the action of other drugs that actually increase blood cholesterol levels due to an interaction with its metabolism. Most experts consider that these are not true interactions, so they will not be dealt with further in this discussion<sup>[13]</sup>

These chemical reactions are also known as pharmacological incompatibilities. The reactions occur when two or more drugs are mixed outside the body of the organism for the purpose of joint administration.<sup>[2]</sup> usually the interactions are antagonistic and it almost always affects both drugs. Examples of these types of interactions include the mixing of penicillin and aminoglycosides in the same serum bottle, which causes the formation of an insoluble precipitate, or the mixing of ciprofloxacin with furosemide. The interaction of some drugs with the transport medium can also be included here. This means that certain drugs cannot be administered in plastic bottles because they bind with the bottle's walls, reducing the drug's concentration in solution.

Many authors do not consider them to be interactions in the strictest sense of the word. An example is the database of the general council of official pharmacists' college of Spain,<sup>[14]</sup> that does not include them among the 90,000 registered interactions

#### Incidence of drug interactions

Among US adults older than 55.4% are taking medications and/or supplements that put them at risk of a major drug interaction.<sup>[32]</sup> Potential drug-drug interactions have increased over time<sup>[33]</sup> and are more common in the low-educated elderly even after controlling for age, sex, place of residence, and comorbidity.<sup>[34]</sup>

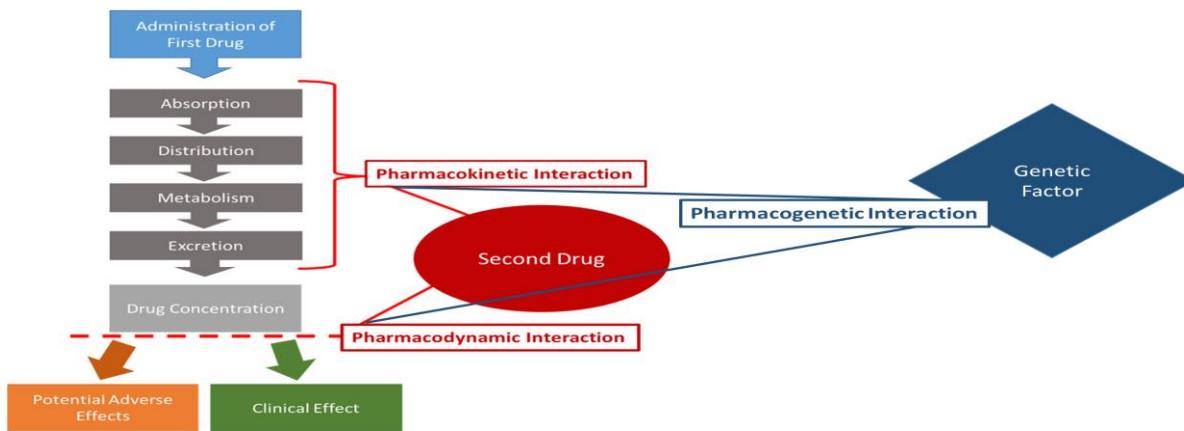
The more drugs a patient takes the greater the likelihood that an adverse reaction will occur. One hospital study found that the rate was 7% in those taking 6–10 drugs but 40% in those taking 16–20 drugs, which represents a disproportionate increase<sup>[35]</sup>.

The simple fact is that some patients experience quite serious reactions while taking interacting drugs, while others appear not to be affected at all.

One French study found that 16% of the prescriptions for a group of patients taking anti-hypertensive drugs were contraindicated or unsuitable,<sup>[36]</sup> whereas another study on a group of geriatrics found only a 1% incidence.<sup>[37]</sup> The incidence of problems would be expected to be higher in the elderly because aging affects the functioning of the kidneys and liver.<sup>[38,39]</sup>

#### Drug-Drug Interactions (DDIs)

DDIs constitute an emerging medical problem around the world, contributing significantly to morbidity and mortality. Generally, unintended interaction between two drugs causes either toxicity or inefficacy; neither of these is a desirable effect. This necessitates alterations in dosage or the pursuit of alternative treatments for therapeutic interventions to avoid the development of clinically significant ADEs. Mechanisms involved in DDIs can be pharmacokinetic (causing alterations in drug exposure), or pharmacodynamic (affecting physiological systems within the body) in nature, or both (Williams & Feely, 2012). Pharmacokinetic interactions have been known to affect drug absorption, distribution, metabolism (biotransformation) and elimination, while pharmacodynamic interactions change the actual effects of a drug (Pleuvry, 2005). Pharmacogenetic factors that contribute to drug interactions constitute a rapidly emerging field of study and involve specific genetic factors that predispose individuals to DDIs via pharmacokinetic or pharmacodynamic mechanisms. The figure shows the general concept of DDIs involving pharmacokinetic and pharmacodynamic mechanisms, as well as the contribution of pharmacogenetic factors.



Unfortunately, DDIs may result in discomfort, debilitating illness, and in extreme cases, death. For instance, when simvastatin (a CYP3A4 substrate) is administered with posaconazole (a CYP3A4 inhibitor), the statin accumulates in the body due to the inhibition of its metabolism by posaconazole, leading to risk of myopathy and rhabdomylosis (Krishna et al., 2012). As illustrated in the previous example, DDIs can cause ADEs, which are associated with morbidity, mortality, and increased healthcare expenditure. As a result, development of methods to avoid these problems

is critical since more accurate and comprehensive information about potential DDIs will increase patient safety as well as health quality. In practice, potential DDIs are challenging to study as they depend on many clinical, environmental, genetic and other factors. In a recent review, Percha & Altman argue that several of these factors work against early identification of potential DDIs (Percha & Altman, 2013). They list the most prohibitive factors as being the lengthy time needed to perform clinical studies and the variance of genetic and demographic features in patient populations, which can produce or hide potential DDIs. In the next section, we will describe existing methods of potential DDI study. (REF D3 PV)

## DRUG INTERACTIONS AND PRECAUTIONS

- Until the role of Echinacea in immune modulation is better defined, this agent should be avoided in patients with immune deficiency disorders (eg, AIDS, cancer), or auto-immune disorder (eg, multiple sclerosis, rheumatoid arthritis).
- Ginkgo may have anti-platelet properties and should not be used in combination with anti-platelet or anti-coagulant medications. Seizures have been reported as a toxic effect of ginkgo, most likely related to seed contamination in the leaf formulations. Uncooked ginkgo seeds or epileptogenic due to presence of ginkgotoxin. Ginkgo formulation should be avoided in individuals with pre-existing seizure disorder.
- Because of reported anti-platelet effects, patients using anti-clotting medications (eg, Warfarin, aspirin, ibuprofen) should use garlic cautiously. Additional monitoring of blood pressure and signs and symptoms of bleeding is warranted. Garlic may reduce the bioavailability of saquinavir, an anti-viral protease inhibitor, but it does not appear to effect the bioavailability of ritonavir.
- Irritability, sleeplessness, and manic behavior have been reported in psychiatric patients using ginseng in combination with other medications (phenelzine, lithium, neuroleptic). Ginseng should be used cautiously in patients taking any psychiatric, estrogenic, or hypoglycemic medications. Ginseng has anti-platelet properties and should not be used in combination with Warfarin. Immune compromised individuals, those taking immune stimulants, and those with auto-immune disorders should use ginseng products with caution.
- Milk thistle does not significantly alter the pharmacokinetics of other drugs transported by the P-glycoprotein transporter or metabolized by Cytochrome enzymes.
- Inhibition of reuptake of various amine transmitters has been highlighted as a potential mechanism of action for St. Johns wort. Drugs with similar mechanism (i.e., anti-depressants, stimulants) should be used cautiously or avoided in patients using St. Johns wort due to the risk of serotonin syndrome. This herb may induce hepatic CYP enzymes and the P-glycoprotein drug transporter.
- No drug-drug interactions have been reported for saw palmetto. Because saw palmetto has no effect on the PSA marker, it will not interfere with prostate cancer screening using this test.
- Co-enzyme Q10 shares a structural similarities with vitamin K, and an interaction has been observed between co-enzyme Q10 and Warfarin. Co-enzyme Q10 supplements may decrease the effects of Warfarin therapy. This combination should be avoided or very carefully monitored.
- Glucosamine sulfate may increase the international normalized ratio (INR) in patients taking Warfarin, increasing the risk for bruising and bleeding. The mechanism is not well understood and maybe dose-related as increases in INR have occurred when the glucosamine dose was increased.
- Melatonin drug interactions have not been formally studied. Various studies, however, suggest that melatonin concentrations are altered by a variety of drugs, including non steroidal anti-inflammatory drugs, anti-depressants, beta-adrenoceptor agonists and antagonists, scopolamine, and sodium valproate. The relevance of these effects is unknown. Melatonin may decrease prothrombin time and may theoretically decrease the effects of Warfarin therapy. Dose-response relationship between the plasma concentrations of melatonin and coagulation activity has been suggested according to one in-vitro analysis. If combination therapy is desired, careful monitoring is recommended especially if melatonin is being used on a short-term basis. Melatonin may interact with nifedipine, possibly leading to increased blood pressure and heart rate. The exact mechanism is unknown.

**Table no-1.6: some important drug interactions:**

Drug or drug group	Properties promoting drug-interaction	Clinically documented interactions
Alcohol	Chronic alcoholism results in enzyme induction. Acute alcoholic intoxication tends to inhibit drug metabolism. Severe alcohol-induced hepatic dysfunction may inhibit ability to metabolize drugs. Disulfiram-like reaction in the presence of certain drugs. Additive CNS depression with other CNS depressants.	<ul style="list-style-type: none"> <li>Acetaminophen:[NE] increased formation of hepatotoxic acetaminophen metabolites</li> <li>Anticoagulants, oral-[NE] increased hypoprothrombinemic effect with acute alcohol intoxication.</li> <li>CNS depressants:[HP] additive or synergistic CNS depression</li> <li>Disulfiram:[HP] inhibited aldehyde dehydrogenase.</li> </ul>
Antacids	Antacids may adsorb drugs in GIT, thus reducing absorption. Antacids tend to speed gastric emptying, thus delivering drugs to absorbing sites in the intestine more quickly. Some antacids alkalinize the urine	<ul style="list-style-type: none"> <li>Digoxin:[NP] decreased GI absorption of digoxin.</li> <li>Ketoconazole:[P] reduced GI absorption of ketoconazole due to increased pH.</li> <li>Tetracyclines:[HP] decreased GI absorption of tetracyclines.</li> </ul>

	somewhat, thus altering excretion of drugs sensitive to urinary pH.	
Anti-coagulants, oral	Warfarin, abixaban, dabigatran, rivaroxaban elimination inducible. Susceptible to inhibition of CYP2C9, CYP3A4 and P-glycoprotein. Warfarin highly bound to plasma proteins. Anticoagulation response altered by drugs that affect clotting factor synthesis or catabolism.	<ul style="list-style-type: none"> <li>Acetaminophen:[NE] impaired synthesis of clotting factors.</li> <li>Chloramphenicol:[NE] decreased dicumarol metabolism.</li> <li>Metronidazole:[P] decreased Warfarin metabolism.</li> <li>Thyroid hormones:[P] enhanced clotting factor catabolism.</li> <li>Phenytoin:[P] dicumarol inhibits metabolism of phenytoin.</li> </ul>
Antidepressants, tricyclic and heterocyclic	Inhibition of amine uptake into postganglionic adrenergic neuron. Antimuscarinic effects may be additive with other anti muscarinic drugs. Metabolism inducible. Susceptible to inhibition of metabolism via CYP2D6, CYP3A4, and other CYP450 enzymes.	<ul style="list-style-type: none"> <li>Amiodarone:[P] decreased anti depressant metabolism.</li> <li>Barbiturates:[P] increased anti depressant metabolism.</li> <li>Carbamazepine:[NP] enhanced metabolism of antidepressants.</li> <li>Guanadrel:[P] decreased uptake of guanadrel into sites of action.</li> <li>Haloperidol:[P] decreased antidepressant metabolism.</li> <li>Quinidine:[NP] decreased antidepressant metabolism.</li> <li>Rifampin:[P] increased antidepressant metabolism.</li> <li>Terbinafine:[P] decreased anti depressant metabolism.</li> </ul>
Barbiturates	Induction of hepatic microsomal drug metabolizing enzymes and P-glycoprotein. Additive CNS depression with other CNS depressants.	<ul style="list-style-type: none"> <li>Beta adreno receptor blockers:[P] increased beta blocker metabolism.</li> <li>Calcium channel blockers:[P] increased <math>Ca^{++}</math> channel blocker metabolism.</li> <li>Delavirdine:[P] increased delavirdine metabolism.</li> <li>Estrogens:[P] increased estrogen metabolism</li> <li>Methadone:[NE] increased methadone metabolism.</li> <li>Phenothiazine:[P] increased phenothiazine metabolism.</li> <li>Quinidine:[P] increased quinidine metabolism.</li> </ul>
Bile acid binding resins	Resins may bind with orally administration drugs in GIT. Resins may bind in GIT with drugs that undergo entero-hepatic circulation, even if the latter are given parenterally	<ul style="list-style-type: none"> <li>Acetaminophen:[NE] decreased GI absorption of acetaminophen.</li> <li>Digitalis glycosides:[NE] decreased GI absorption of digitoxin (possibly also digoxin)</li> <li>Furosemide:[P] decreased GI absorption of furosemide.</li> <li>Methotrexate:[NE] reduced GI absorption of methotrexate.</li> <li>Thiazide diuretics:[P] reduced GI absorption of thiazides.</li> </ul>
Calcium channel blockers	Verapamil, diltiazem, and perhaps nicardipine inhibit hepatic drug metabolizing enzymes and P-glycoprotein. Metabolism (via CYP3A4) of diltiazem, felodipine, nicardipine, nifedipine, verapamil, and probably other calcium channel blockers subject to induction and inhibition.	<ul style="list-style-type: none"> <li>Atazanavir:[NE] decreased metabolism of calcium channel blockers.</li> <li>Cimetidine:[NP] decreased metabolism of calcium channel blockers.</li> <li>Erythromycin:[P] decreased metabolism of calcium channel blockers.</li> <li>Phenytoin:[P] increased metabolism of calcium channel blockers.</li> <li>Rifampin:[P] increased metabolism of calcium channel blockers.</li> <li>Sirolimus:[P] decreased sirolimus elimination with diltiazem, nicardipine, verapamil.</li> <li>Tacrolimus:[P] decreased tacrolimus elimination with diltiazem, nicardipine, verapamil.</li> </ul>
Chloramphenicol	Inhibits hepatic drug metabolizing enzymes.	<ul style="list-style-type: none"> <li>Phenytoin:[P] decreased phenytoin metabolism.</li> <li>Sulfonylurea hypoglycemic:[P] decreased sulfonylurea metabolism</li> </ul>
Disulfiram	Inhibits CYP2C9. Inhibits aldehyde dehydrogenase.	<ul style="list-style-type: none"> <li>Benzodiazepines:[P] decreased metabolism of chlordiazepoxide and diazepam but not lorazepam and oxazepam.</li> <li>Metronidazole:[NE] confusion and psychoses reported in patients receiving this combinations; mechanisms unknown.</li> <li>Phenytoin:[P] decreased phenytoin metabolism.</li> </ul>
Estrogens	Metabolism inducible. Entero-hepatic circulation of estrogen may be interrupted by alteration in bowel flora(eg, due to antibiotics).	<ul style="list-style-type: none"> <li>Ampicilline:[NP] interruption of entero-hepatic circulation of estrogen; possible reduction in OC efficacy. Some other oral antibiotics may have similar effects.</li> <li>Bosentan:[NP] enzyme induction leading to reduced estrogen effect.</li> <li>Corticosteroids:[P] decreased metabolism of corticosteroids leading to increased corticosteroid effect.</li> </ul>

		<ul style="list-style-type: none"> <li>Griseofulvin:[NE] increased estrogen metabolism, possible reduction in OC efficacy.</li> <li>Phenytoin:[P] increased estrogen metabolism; possible reduction in OC efficacy.</li> <li>Rifabutin:[P] increased estrogen metabolism; possible reduction in OC efficacy.</li> <li>St.John's wort:[P] increased estrogen metabolism; possible reduction in OC efficacy.</li> </ul>
Iron	Binds with drugs in GIT, reducing absorption	<ul style="list-style-type: none"> <li>Methyldopa:[NE] decreased methyldopa absorption.</li> <li>Quinolones:[P] decreased absorption of ciprofloxacin and other quinolones.</li> <li>Tetracyclines:[P] decreased absorption of tetracyclines; decreased efficacy of iron.</li> </ul>
Levodopa	Levodopa degraded in gut prior to reaching sites of absorption. Agents that alter GI motility may alter degree of intra-luminal degradation. Anti-parkinsonism effect of levodopa susceptible to inhibition by other drugs.	<ul style="list-style-type: none"> <li>Clonidine:[NE] inhibited anti-parkinsonism effect</li> <li>MAO-inhibitors:[P] hypertensive effect (carbidopa prevents the interaction)</li> <li>Phenothiazines:[P] inhibited anti-parkinsonism effect</li> </ul>
Macrolides	The macrolides clarithromycin and erythromycin are known to inhibit CYP3A4 and P-glycoprotein. Azithromycin doesn't appear to inhibit CYP3A4 but is a modest inhibitor of P-glycoprotein	<ul style="list-style-type: none"> <li>Benzodiazepines:[P] decreased metabolism of alprazolam, midazolam, triazolam.</li> <li>Ergot alkaloids:[P] decreased elimination of ergot alkaloids</li> <li>Phosphodiesterase inhibitors:[P] decreased metabolism of phosphodiesterase inhibitor.</li> <li>Quinidine:[P] increased serum quinidine concentrations.</li> <li>Theophylline:[P] decreased metabolism of theophylline.</li> </ul>
NSAIDS	Prostaglandin inhibition may result in reduced renal sodium excretion, impaired resistance to hypertensive stimuli, and reduced renal lithium excretion. Most NSAIDS inhibit platelet function; may increase likelihood of bleeding due to other drugs that impair hemostasis.	<ul style="list-style-type: none"> <li>ACE inhibitors:[P] decreased anti-hypertensive response.</li> <li>Furosemide:[P] decreased diuretic, natriuretic, and hypertensive response to furosemide.</li> <li>Hydralazine:[NE] decreased anti-hypertensive response hydralazine.</li> <li>Methotrexate:[NE] possibly increase methotrexate toxicity (especially anti-cancer doses of methotrexate)</li> <li>SSRIs: increased risk of bleeding due to platelet inhibition.</li> <li>Thiazide diuretics: [P]decreased diuretic, natriuretic, and antihypertensive response.</li> </ul>
Pimozide	Susceptible to CYP3A4 inhibitors; may exhibit additive effect with other agents that prolong QTc interval.	<ul style="list-style-type: none"> <li>Nefazodone:[NE] decreased pimozide metabolism.</li> </ul>
Probenicid	Interference with renal excretion of drugs that undergo active tubular secretion, especially weak acids. Inhibition of glucuronide conjugation of other drugs.	<ul style="list-style-type: none"> <li>Clofibrate:[P] reduced glucuronide conjugation of clofibrate acid.</li> <li>Methotrexate:[P] decreased renal methotrexate excretion; possible methotrexate toxicity.</li> <li>Pralatrexate:[P] decreased renal pralatrexate excretion; possible pralatrexate toxicity.</li> <li>Penicillin:[P] decreased renal penicillin excretion</li> <li>Salicylates:[P] decreased uricosuric effect of probenicid (interaction unlikely with less than 1.5g of salicylate daily).</li> </ul>
Quinolone antibiotics	Susceptible to inhibition of GI absorption. Some quinolones inhibit CYP1A2.	<ul style="list-style-type: none"> <li>Caffeine:[P] Ciprofloxacin, enoxacin, pipemidic acid, and, to a lesser extent, norfloxacin inhibit caffeine metabolism.</li> <li>Sucralfate:[P] reduced GI absorption of ciprofloxacin, norfloxacin, and probably other quinolones.</li> </ul>
SSRIs	SSRIs can lead to excessive serotonin response when administered with other serotonergic drugs (eg, MAOIs). Some SSRIs inhibit various CYP450s including CYP2D6, CYP1A2, CYP3A4, and CYP2C19.	<ul style="list-style-type: none"> <li>Theophylline:[P] decreased metabolism of theophylline by fluvoxamine-induced inhibition of CYP1A2.</li> </ul>
Theophylline	Susceptible to inhibition of hepatic metabolism by CYP1A2. Metabolism inducible.	<ul style="list-style-type: none"> <li>Diltiazam:[NP] decreased theophylline metabolism.</li> <li>Smoking:[HP] increased theophylline metabolism.</li> <li>Tacrine:[NP] decreased theophylline metabolism.</li> </ul>

**METHODOLOGY:****Study design:**

It is a prospective observational study includes the detection of drug interactions, improving the drug safety access and therapeutic outcome of either sex and age between 18 to all age groups from inpatients of all departments of Santhiram medical college and general hospital in Nandyal, Kurnool dist, andhrapradesh.

**Study period:** From june 2017-February 2018 – 9months

**Study population:**

Population of the study includes the patients who are undergoing the treatment in a tertiary care teaching hospital.

**Number of patients:** approximately 100-150

**Collection of data:**

- By reviewing case sheets
- By interacting with patients
- By reviewing prescriptions.
- By interacting with health care professionals.
- By ward round participation.

## STUDY CRITERIA

**Inclusion criteria:**

- The patients who are admitted to the tertiary care teaching hospital are included in the study.
- Patients are included in the study with detailed informed consent forms.

**Exclusion criteria:**

- The patients who comes under the age below 18 years are excluded from the study.
- The patients who are not admitted in the hospital i.e out-patients are excluded from the study.

## TIME LINE:

1. Phase I (1month)
  - Selection of topic
  - Preparation of protocol
  - Ethical committee approval
  - selection of patient by reviewing case reports.
2. Phase II (7months)
  - Selection of patient by reviewing case reports.
  - Regular follow up of patients.
  - Patient counseling.
  - pharmacist intervention.
3. Phase III (1 month)
  - Result calculation based on statistical analysis
  - Thesis preparation
  - Planning for publication and submission

## STATISTICAL ANALYSIS

The collected data from the specially designed proforma are entered into excel sheets, suitable statistics are applied to project the results.

## Results:

The prospective observational study was conducted for a period of six months from July to December 2017 in all inpatient departments at a tertiary care teaching hospital, Nandyal.

**Table No 5.1: Gender wise distribution**

SL.NO	Gender	No of patients	Percent(%)
1	Male	63	58.3
2	Female	45	41.7
3	Total	108	100

## SEX DISTRIBUTION

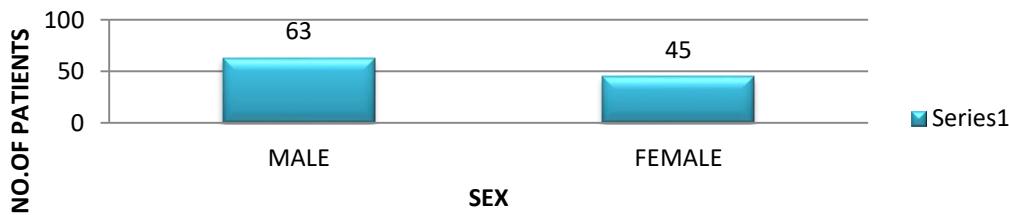


Figure No. 1: Gender wise distribution

Among 108 patients male patients are more 63(58.3%) when compared to female patients.

Table No 5.2: Age wise distribution of patients.

SL.NO	Age(years)	No of Patients	Percent(%)
1	<20	7	6.5
2	21-30	9	8.3
3	31-40	14	13.0
4	41-50	15	13.9
5	51-60	14	13.0
6	61-70	32	29.6
7	71-80	16	14.8
8	81-90	1	0.9
9	Total	108	100

## AGE DISTRIBUTION

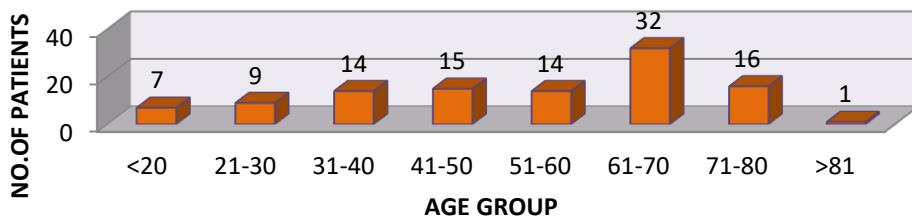


Figure No. 2: Age wise distribution of patients.

We divided patients according to age group in that 61-70 years of age group were more 32(29.6%) followed by 71-80 i.e. 16(14.8%) , 15(13.9%), 14(13.0%), 14(13.0%), 9(8.3%), 7(6.5%), 1(0.9%) are seen in 71-50, 41-50, 51-60, 31-40, 21-30, <20, >81 years of age of patients respectively.

Table No 5.3: drug-drug interactions

SL.NO	Frequency	Percent
1	Present	56
2	Absent	52
3	Total	108

Among 108 cases, 56(51.9%) cases may have drug-drug interaction

## DRUG-DRUG INTERACTIONS

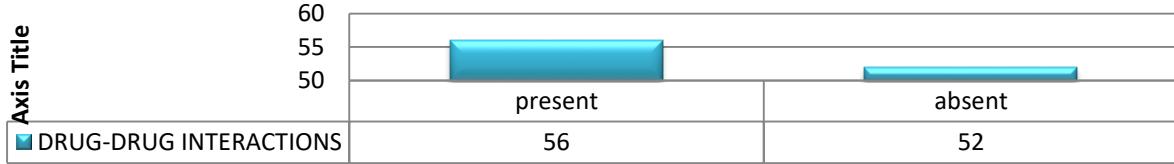


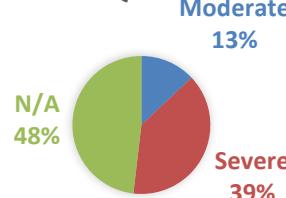
Figure no 5.3 DRUG-DRUG INTERACTIONS

Table No 5.4: Severity of drug-drug interactions

SL.NO	Frequency	Percent
1	Moderate	14
2	Severe	42
3	N/A	52
4	Total	108

Among 108 cases, 42(38.9%) may have severe Drug-Drug interactions.

## FREQUENCY



SL.NO	Frequency	Percent
1	Present	75
2	Absent	33
3	Total	108

Figure no 5.4 Severity of drug interactions

Table No 5.5: DRUG-FOOD INTERACTIONS

Among 108 cases, 75(69.4%) cases may have drug-food interactions.

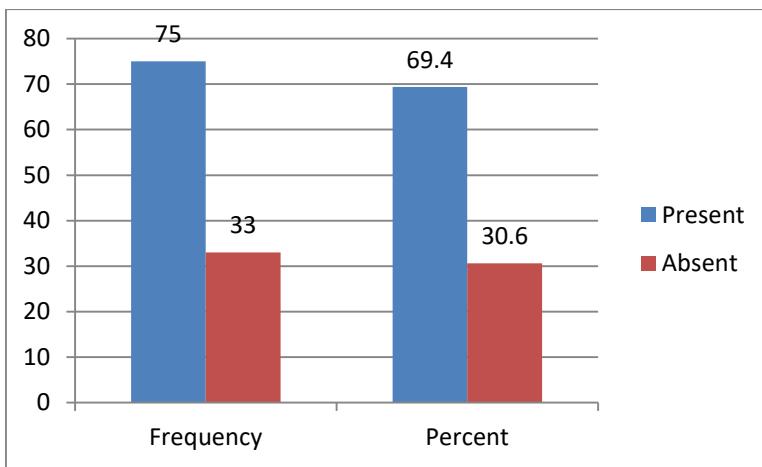


Figure no 5.5 drug-food interactions

Table No 5.6: Severity of drug food interactions

Among 108 cases, 52(48.1) cases may

SL.NO		Frequency	Percent
1	Moderate	52	48.1
2	Severe	23	21.3
3	N/A	33	30.6
4	Total	108	100.0

have moderate drug-food interactions.

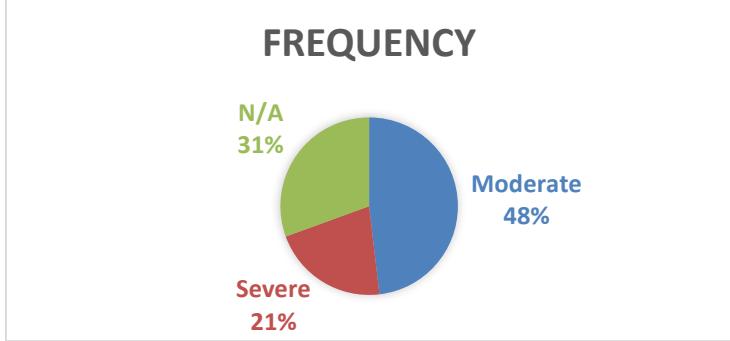


Table No 5.7: DRUG-HERBAL INTERACTIONS

Among 108 cases, no case found having drug-herbal interactions.

Figure 5.6 severity of drug-food interactions

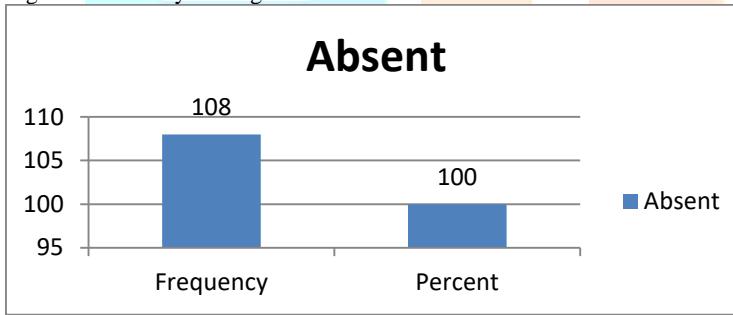


Table No 5.8: Severity of Drug-herbal interactions

Among 108 cases, no cases were found with drug-herbal interactions

SL.NO		Frequency	Percent
1	Absent	108	100.0

Table No 5.9: DRUG-ETHANOL INTERACTIONS

SL.NO		Frequency	Percent
1	Present	16	14.8
2	Absent	92	85.2
3	Total	108	100.0

Among 108 cases, 16(14.8%) cases may have drug-ethanol Interactions.

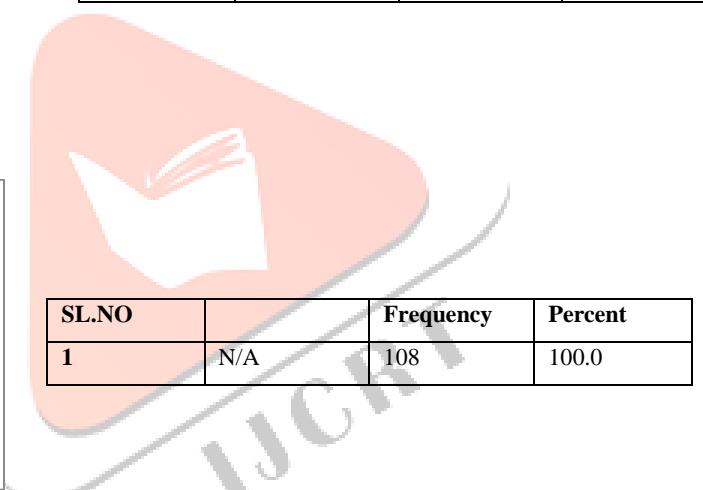
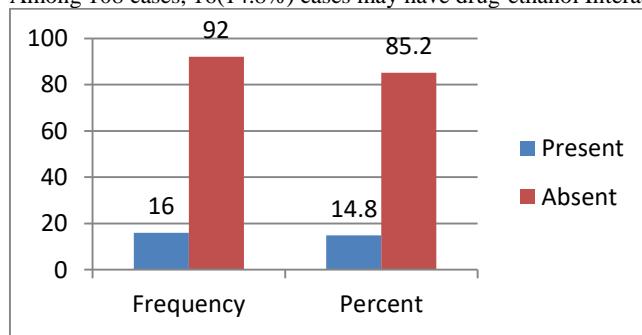
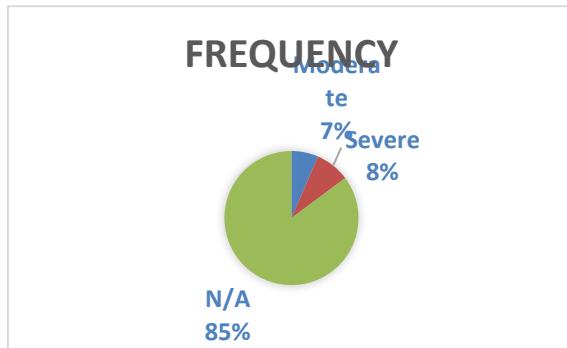


Table No 5.10: severity of Drug-ethanol interactions

Among 108 cases, 9(8.3) may have severe drug-ethanol interacti

SL.NO		Frequency	Percent
1	Moderate	7	6.5
2	Severe	9	8.3
3	N/A	92	85.2
4	Total	108	100.0

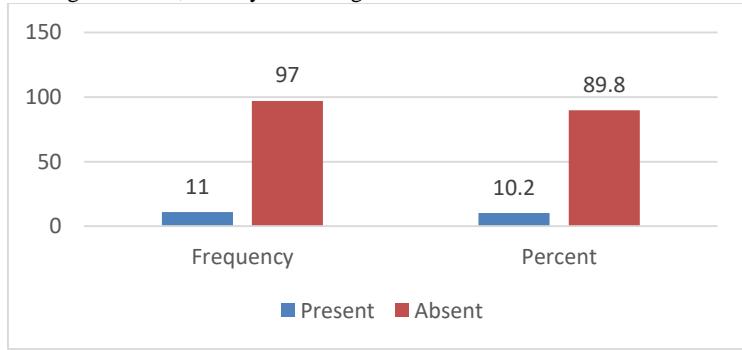


SL.NO		Frequency	Percent
1	Present	11	10.2
2	Absent	97	89.8
3	Total	108	100.0

Figure 5.10: severity of drug-ethanol interactions

**Table No 5.11: DRUG-LABORATORY INTERACTIONS**

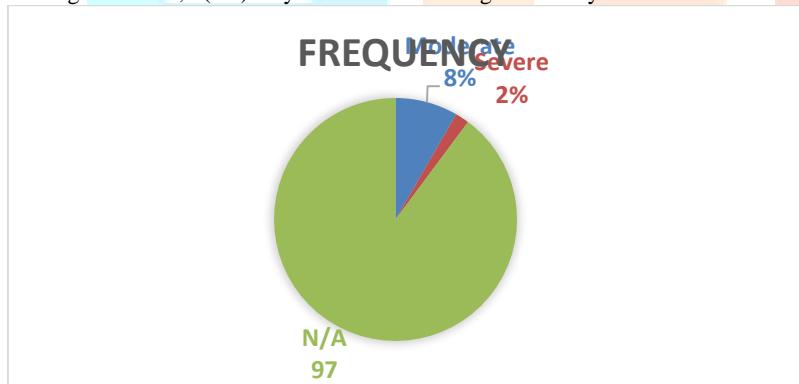
Among 108 cases, 11 may have drug-herbal Interactions.



SL.NO		Frequency	Percent
1	Moderate	9	8.3
2	Severe	2	1.9
3	N/A	97	89.8
4	Total	108	100.0

**Table No 5.12: Severity of Drug-laboratory interactions**

Among 108 cases, 9(8.3) may have moderate drug-laboratory interactions



SL.NO		Frequency	Percent
1	Present	11	10.2
2	Absent	97	89.8
3	Total	108	100.0

Figure 5.12: severity of DRUG-LABORATORY interactions

**Table No 5.13: Drug-Tobacco interactions**

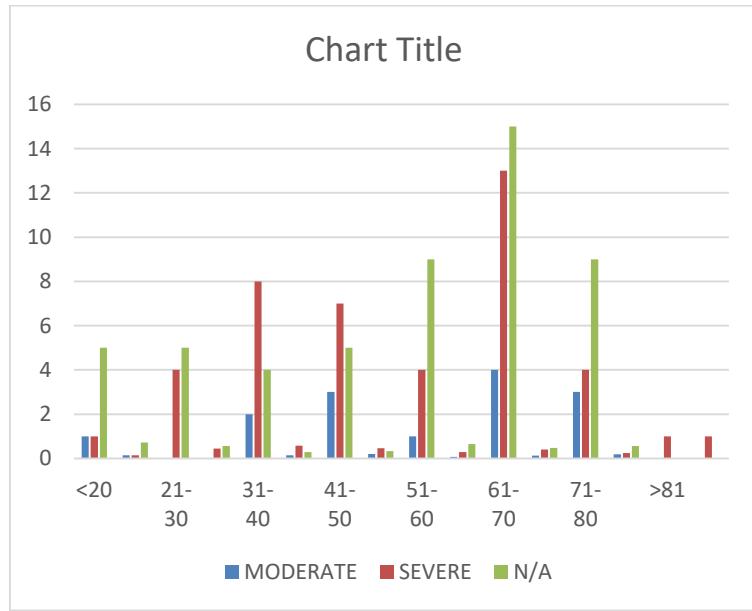
Among 108 cases, 11 cases may present Drug-Tobacco Interactions.

**Table No 5.15: Severity of Drug-Drug Interaction in Different Age Groups**

AGE GROUPING (YEARS)	MODERATE	SEVERE	N/A	TOTAL
<20	1 14.3%	1 14.3%	5 71.4%	7 100%
21-30	0 0.0%	4 44.4%	5 55.6%	9 100.0%
31-40	2 14.3%	8 57.1%	4 28.6%	14 100%
41-50	3 20.3%	7 46.7%	5 33.3%	15 100%
51-60	1 7.1%	4 28.6%	9 64.3%	14 100%
61-70	4 12.5%	13 40.6%	15 46.9%	32 100%
71-80	3 18.3%	4 25.0%	9 56.3%	16 100%
>81	0 0.0%	1 100.0%	0 0.0%	1 100%

Total	14 13.0%	42 38.9%	52 48.1%	108 100%
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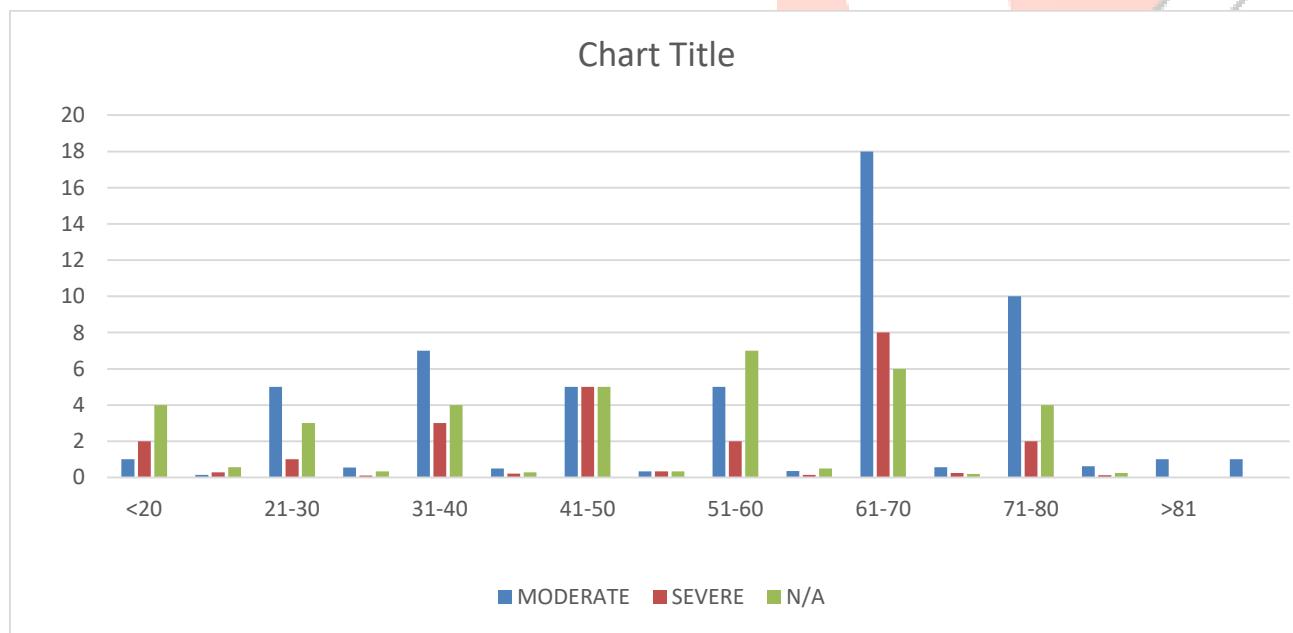
Among 108 Patients Moderate Drug-Drug interactions are more in the 61-70 years age group patients and severe Drug-Drug Interactions are more in the 61-70 years age group Patients.

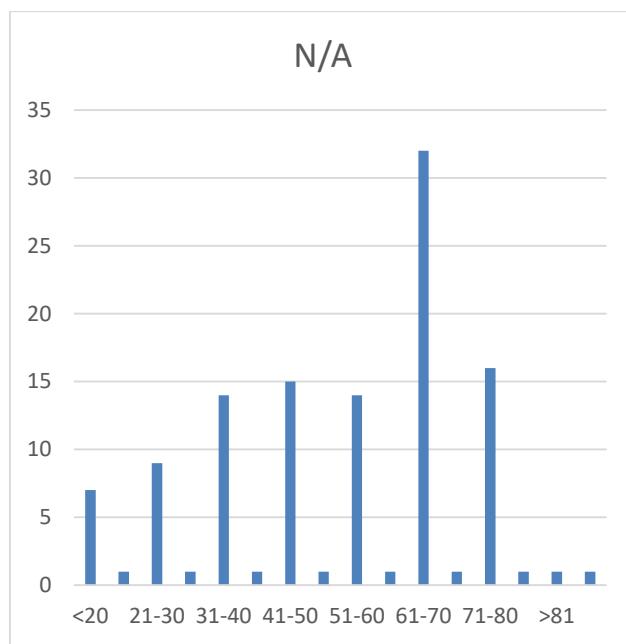


AGE GROUPING (YEARS)	MODERATE	SEVERE	N/A	TOTAL
<20	1 14.3%	2 28.6%	4 57.1%	7 100%
21-30	5 55.6%	1 11.1%	3 33.3%	9 100.0%
31-40	7 50%	3 21.4%	4 28.6%	14 100%
41-50	5 33.3%	5 33.3%	5 33.3%	15 100%
51-60	5 35.7%	2 14.3%	7 50.0%	14 100%
61-70	18 56.3%	8 25%	6 18.8%	32 100%
71-80	10 62.5%	2 12.5%	4 25.0%	16 100%
>81	1 100%	0 0%	0 0.0%	1 100%
Total	52 48.1%	23 21.3%	33 30.6%	108 100%

Table No.13: Severity of Drug-Food Interactions in Different Age groups

Among 108 patients moderate Drug-Food interactions are more in the 61-70 years age group patients and severe Drug-Food interactions are more in the 61-70 age group patients.





Among 108 patients moderate Drug-Ethanol interactions are more in 61-70 years age group patients and severe Drug-Ethanol interactions are more in 31-40 years age group.

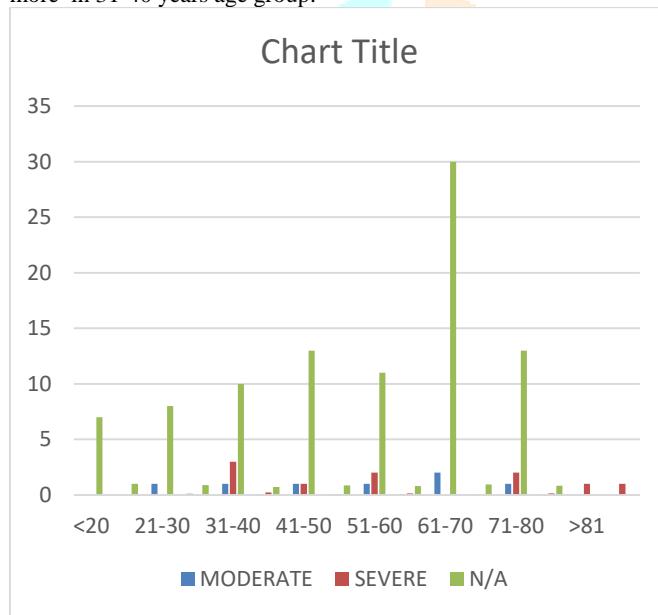


Table no.16:

Among 108 patients moderate drug-laboratory interactions are more in 61-70 years age group patients and severe drug-laboratory interactions are equal in 21-30 and 61-70 years age group.

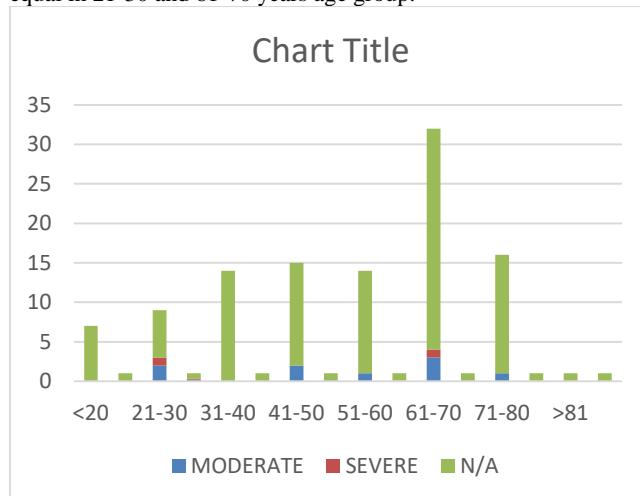
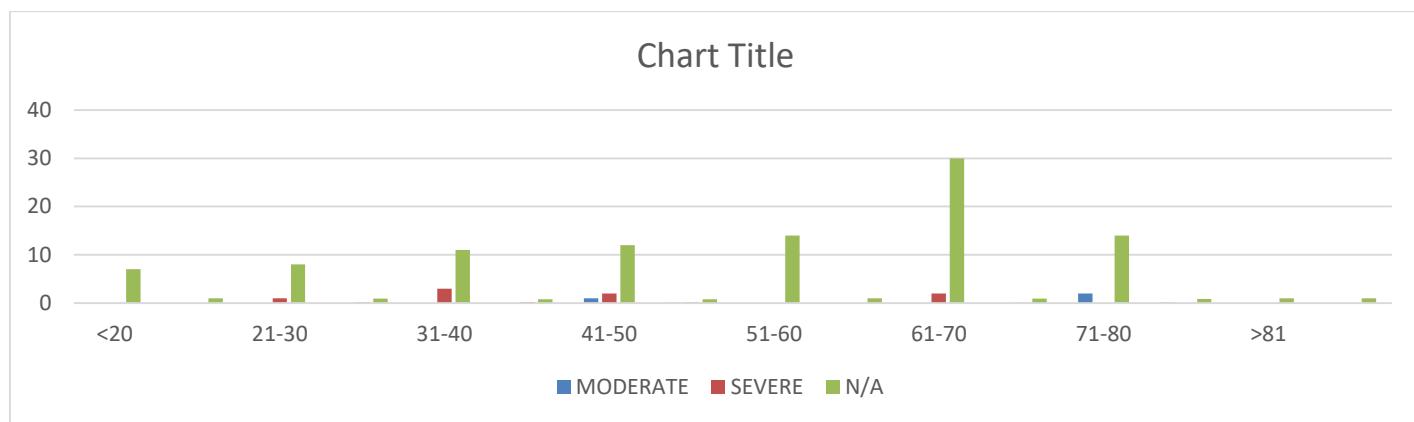


Table no.17:

Among 108 patients moderate Drug-Tobacco interactions are more in 71-80 years age group patients and severe Drug-Tobacco interactions are more in 31-40 years age group patients.

	N/A	Total
UPING(YEARS)		
<20	7 100.0%	7 100%
21-30	9 100.0%	9 100.0%
31-40	14 100.0%	14 100%
41-50	15 100.0%	15 100%
51-60	14 100.0%	14 100%
61-70	32 100.0%	32 100%
71-80	16 100.0%	16 100%
>81	1 100.0%	1 100%
Total	108 100%	108 100%

AGE GROUPING(YEARS)	MODERATE	SEVERE	N/A	TOTAL
<20	0 0.0%	0 0.0%	7 100.0%	7 100%
21-30	2 22.2%	1 11.1%	6 66.7%	9 100.0%
31-40	0 0.0%	0 0.0%	14 100.0%	14 100%
41-50	2 13.3%	0 0.0%	13 86.7%	15 100%
51-60	1 7.1%	0 0.0%	13 92.9%	14 100%
61-70	3 9.4%	1 3.1%	28 87.5%	32 100%
71-80	1 6.3%	0 0.0%	15 93.8%	16 100%
>81	0 0.0%	0 0.0%	1 100.0%	1 100%
Total	9 8.3%	2 1.9%	97 89.8%	108 100%



Drug – drug interactions  
 Diclofenac – furosemide  
 Diclofenac – hydrocortisone  
 Metronidazole – ondansetron  
 Acetaminophen – ondansetron  
 Aspirin – digoxin  
 Haloperidol – olanzapine  
 Deflazacort – Diclofenac  
 Pantoprazole – ferrous fumarate  
 Albuterol – ipratropium bromide  
 Forecox – deflazacort

2 times

## DISCUSSION

This study included 108 patients which were included from all the departments of inpatients in a tertiary care teaching hospital. Parameters like old age, gender, poly pharmacy, genetic factors, pharmacokinetic factors and co-morbid conditions were mainstay for data collection process. These parameters were isomeric with that of the five articles (i.e.) collected from standard journals concluding drug interaction patterns in patients.

The incidence of potential DDIs during the pre-intervention phase of our study was 53%. A review of nine epidemiological studies had an increase ranging from 0% to 2.8%. Similarly, a study from the United States reported interactions to be responsible for nearly 2% of adverse events in acute hospitalizations. A community study including 962013 prescriptions in Sweden reported an incidence of 13.6%. Another south Indian study from a community pharmacy reported an incidence of 26%. The reason for higher incidence in our study could be due to the inclusion of patients from internal medical wards and ICU, where usually chronically ill and patients with multiple complications requiring polypharmacy are admitted.

Among all those 108 patients collected for the study, the incidence of interactions were observed more in male patients (58.3%) compared to female patients (41.7%).

Among all those 108 patients collected for the study, the incidence of interactions with respective to age were observed more in 61 – 80 years age group accounting to 42.59% followed by 41 – 60 years of age group accounting to 25%, which follows 21 – 40 years of age group accounting to 23.14%, followed by <20 years of age group accounting to 6.48%, where the least occurrence of interactions were found in the age group of above 80 years i.e. 2.7%. The more number of interactions were found in age group of 61 – 80 years age group due to factors relating to human physiology changes with age may affect the interaction of drugs.

We found the incidence of potential DDIs was higher in the age group of 61-80 years age group. Confirming to other studies we also observed an increase in the number of potential DDIs with age. Similarly a study from Sweden reported 31% of the DDIs in elderly patients. This is because elderly patients use more medications as part of normal drug regimen

The present study observed that poly pharmacy was common (7.85 drugs per prescription). A study by smith et al found an ADR rate of 7% in patients taking 6-10 drugs increasing to 40% in those taking 16-20 drugs. A study conducted in the USA found the increasing in the risk of adverse drug interactions from 13% for patients taking two medications to 82% for those taking 7 or more medications. In our study we have observed more number of interactions was found in the patients who are taking 6-10 drugs (i.e. 54.7%). Our study population included both critically ill and elderly patients. Elderly patients require a greater number of drugs.

We found 54.62% of the potential drug interactions to be major severity type. Moderately severity type account for 55.38% of DI's. Our values are higher than the findings reported from a study conducted in the US, which reported 7.3% of major DDIs in a surgical intensive care unit. In our study DIs are differentiated into drug-drug, drug-food, drug-laboratory, drug-ethanol, drug-tobacco. Among these drug-food interactions(40.74%) are more seen in our study and then drug-drug interactions(35.18%), drug-ethanol(9.25%), drug-tobacco(5.55%), and last drug-laboratory(3.70%) interactions.

In our study we differentiated the number of interactions per patient. Majorly four interactions per patient were shown in 5 patients. Three interactions per patient were shown in 15 patients. Two interactions per patient were shown in 39 patients. Two interactions per patient were shown in 33 patients. Finally there are no interactions were observed in 16 patients.

In our study, majority of the potential DIs had a delayed onset as per the micromedex electronic database. In general, DIs usually have a specific time course i.e. onset and duration and this makes them more predictable and preventable than ADRs. This finding suggests that one should be careful while prescribing drugs that can cause delayed type of DIs. These patients should also be counseled for careful monitoring of symptoms suggestive of the occurrence of DIs. There was no significant reduction in the onset type after the intervention.

## CONCLUSION

The study found the associations of potential DIs with age, sex, number of drugs per prescription. There was a direct link between polypharmacy and occurrence of DIs. To lower the frequency of potential interactions it could be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events. The study concluded that educational interventions can minimize the incidence of DIs.

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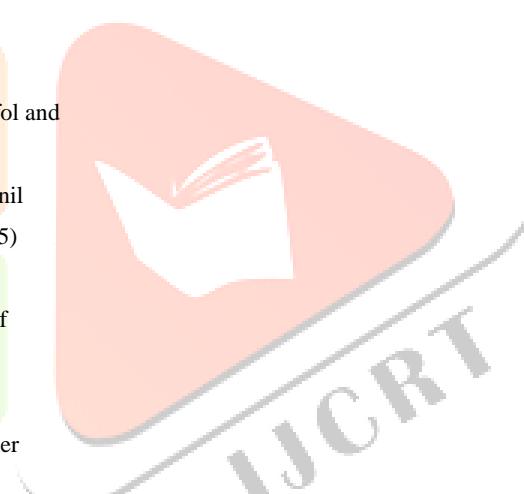
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