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Drug-Drug Interactions: How Far It Can Be Prevented?

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ABSTRACT

Drug-drug interaction is a matter of deep concern as this proves to be the major cause of adverse drug reaction (ADR). It may be on pharmacokinetic or pharmacodynamic level. Pharmacokinetic interactions involve the effect of absorption, distribution, metabolism and excretion whereas pharmacodynamic interactions emphasize mainly on three areas viz., interactions that occur at single receptor site, at variety of receptor sites and general non-specific interactions mediated through unspecified sites of action. Different factors are responsible such as genetic constitution, disease, diet, pharmacological response and polypharmacy, age related physiological changes on the basis of the outcomes obtained on the clinical effects of the drug used. This article reflects a clear picture on drug-drug interactions for cytochrome p-450 and non steroidal anti-inflammatory drug (NSAIDs), antihistaminic drugs, antidepressants, interactions with antiretrovirals and Rifampin, anti-anaemic agents, dermatological drugs, antipsychotic drugs, major antibiotics, sedative-hypnotic and anti-cancer drugs.

Keywords: Adverse drug reaction (ADR), Drug-drug interactions, Polypharmacy, Cytochrome, Drug monitoring.

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INTRODUCTION

Drug interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or some environmental chemical agent (Baxter 2005). The net effect of the combination may manifest as an additive or enhanced effect of one or more drugs, antagonism of the effect of one or more drugs, or any other alteration in the effect of one or more drugs. Drug interactions are an important cause of adverse drug reaction (ADR) which was recognized over 100 years ago, when it was noted that an adrenal extract, when given to a dog anaesthetized with chloroform, could cause arrhythmias. Today, with the increasing availability of complex therapeutic agents and widespread polypharmacy, the potential of drug interaction is enormous[1]. It has been estimated that patients in hospital, who are receiving more than 6 drugs at a time, have a 6 to 7 times greater incidence of adverse effects including those due to drug interactions than those who are receiving less than 6 drugs. Also about 7% of all adverse drug reactions are estimated to be due to adverse drug interactions, and account for approximately one-third of the mortality of such patients. The elderly are more prone to drug interactions, not only because they receive more drugs than younger patients, but because in them the pharmacokinetics of drugs are different[2]. The major changes in the action of a drug, for which the key factor is drug interactions is a topic of concern. The same type of interaction can not be expected in every individual as there are various factors that can be the cause for a known interaction to occur in an individual. These factors can be due to differences in the genes, physiology, age, diet and exercise, diseased condition, dosing, and if a combined therapy is given; the duration and relative time of administration of two drugs. The frequent occurrence of these drug interactions is a serious blow to the health care sector as millions of dollars get added to the respective cost and many drugs get withdrawn because of interaction with other drugs causing serious health issues[1]. Current approaches to drug-drug interactions discovery, which include phase IV clinical trials answer post marketing surveillance, are insufficient to detect many drug-drug interactions an do not alert the public potentially dangerous drug-drug interactions before a drug enters the market. Recent work has applied state-of-the-art computational and statistical methods to the problem of drug-drug interaction[1].

Factors Affecting Drug Interactions

There is little, that science can do to age-related physiological changes, genetic constitution, pharmacological responses and diseases in terms of drug interactions where as diet can be controlled to avoid interactions. It is the polypharmacy factor (or multiple drug usage) that drug-

drug interactions studies have to take care of. Johnell did an extensive study regarding effect of polypharmacy usage in the elderly. The study indicates a direct correlation between number of drugs used and clinically relevant Type C and Type D drug-drug interactions[5]. Prevalence of potentially clinically relevant Type C drug-drug interactions (DDIs) as a function of number of dispensed drugs among 630743 people aged ≥ 75 years from the Swedish Prescribed Drug Register, 2005. A more thorough study based on each type of Adverse Drug Reaction as done in the case of diabetes patients is required to be performed in groups with co-morbidities for further analysis of reasons underlying DDIs[3].

Mechanism of Drug Interactions

Pharmacokinetic Interaction

The last two decades, have been years of rising concern on pharmacokinetic drug interaction. These include the selective serotonin reuptake inhibitor (SSRI) and related mixed mechanism antidepressants, novel azole antifungal agents, newer macrolide antimicrobial agents, and the highly active antiretroviral therapies (HAART) used against human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). While these and other classes of agents have had a major beneficial impact of the therapy on some serious and life threatening illnesses, many of the agents have the secondary pharmacologic property of inhibiting the human cytochrome P450 (CYP) enzymes responsible for oxidative metabolism of most drugs used in clinical practice[4-19].

Nomenclature

A useful although legalistic nomenclature system refers to the agent causing the drug interaction as the ‘‘perpetrator,’’ while the drug being affected by the interaction is the ‘‘victim’’. Drug interaction on a pharmacokinetic level means that there could be a change in the concentration of the victim drug in the plasma as well as the site of action and this is because the perpetrator is responsible for the change in the metabolic clearance of the victim. It might not change the clinical activity of the victim drug. Modification in the access of victim to its pharmacological receptor site but no change to the systemic clearance or plasma levels of victim by the perpetrator is defined as pharmacokinetic interaction “variant”. An example is flumazenil act as an antagonist to benzodiazepine activity. In pharmacodynamic interaction there is either inhibition or enhancement of the clinical effects on a victim drug due to identical end-organ actions[20-23].

Inhibition vs. Induction of metabolism

Mechanistically different processes are involved in drug interactions involving inhibition as opposed to induction of metabolism mediated by CYP enzymes. Chemical inhibition is an

immediate phenomenon; the effect becomes evident as soon as the inhibitor comes in contact with the enzyme and is in principle reversible when the inhibitor is no longer present. The magnitude of inhibition i.e., the size of the interaction—depends on the concentration of the inhibitor at the intra-hepatic site of enzyme activity relative to the intrinsic potency of the inhibitor. Inhibition potency can be measured using in vitro systems, yielding quantitative estimates such as the inhibit ion constant (Ki) or the 50% inhibitory concentration (IC50)[24-33].

Table 1: Mechanistic Comparison of CYP Inhibition and Induction

	Inhibition	**Induction**
Mechanism	Direct chemical effect on enzyme.	Indirect effect through enhanced production of CYP protein.
Onset & reversibility	Rapid	Slow
Immediate exposure	Needed	Not needed
Prior exposure	Not needed	Needed
In vitro study	Straight forward	Difficult

Pharmacodynamic Interaction

The pharmacodynamic interaction generally occurs between drug which have either additive or opposing effects and the brain is commonly affected organ due to this interaction. For e.g., adding tramadol to selective serotonin reuptake inhibitor (SSRI) causes serotonin syndrome. Opposite to this concept there is a loss of drug effect when drugs are combined of opposite effects for e.g., b2 agonist with non selective b blocker; there is reduced bronchodilation[14].

Clinical Importance of Drug Interactions

Given the prevalence of polypharmacy in clinical practice, non interactions of drugs are far more common than interactions. The usual outcome of co-administration of two drugs is no detectable pharmacokinetic or pharmacodynamic interaction. That is, the pharmacokinetic disposition and clinical activity of each drug proceeds independent of each other. Less common is the occurrence of a kinetic interaction. That is detectable using controlled study design methods but is of no clinical importance under usual therapeutic circumstances because the interaction, while statistically significant, is not large enough in magnitude to produce a clinically important change in dynamics of the victim drug; the therapeutic index of the victim drug is large enough that even a substantial change in plasma levels of the victim will not alter therapeutic effects or toxicity; or kinetics and response to the victim drug is so variable that changes in plasma levels due to the drug interaction are far less important than inherent variability. Even less common are clinically important interactions that require modification in dosage of the perpetrator, the victim, or both. The most unusual consequence of a drug interaction is a situation in which the drug combination is

so hazardous as to be contraindicated, as in the case of ketoconazole and terfenadine. These situations are rare, but unfortunately they receive disproportionate attention in the public media[34-36].

Table 2: **Some additive or synergistic interactions[1]**

Interacting Drug	Pharmacological Effect
NSAID, warfarin, clopidogrel	Increased risk of bleeding.
ACE inhibitors and K-sparing diuretics	Increased risk of hyperkalaemia.
Verapamil abd β-adrenargic antagonists	Bradycardia and asystole.
Neuromuscular blockers and aminoglycosides	Increased neuromascular blockade.
Alcohol and benzodiazepines	Increased sedation.
Thioridazine and sotalol	Increased risk of QT interval prolongation.
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Drug– Drug Interactions

Table 3: Drug interaction with cytochrome p450 enzymes [37]

CYP P450 enzyme	Inhibitor	Inducer
CYP1A2	**Ciprofloxacin, Fluvoxamine**, Ethinyloestradiol, Interferon A-2b	Phenytoin, Rifampicin
CYP2C9	Fluconazole	Carbamazapine, Rifampicin
CYP2C19	**Fluconazole, Fluvoxamine, Fluoxetine**, Fluconazole, Clarithromycin, Voriconazole, Moclobemide	Iopinavir/Ritonavir, Rifampicin,
CYP2D6	**Bupropion, Fluoxetine, Peroxetine, Perhexiline,** Cinacalcet, Doxepin, Duloxetin, Flecainide, Moclobemide, Quinine, Terbinafine	
CYP3A	**Macrolide - Erythromycin, Clarithromycin Azole Antifungals - Vericonazole, Itraconazole, Ketoconazole,** Fluconazole, Posaconazole **Protease Inhibitor - Indinavir, Ritonavir, Saqulnavir,** Atazanavir, Fosamprenavir, Non-dehydropyridine calcium channel blocker - Diltiazem, Verapamil	Carbamazepine, Modafinil, Phenytoin, Phenobarbitone, Rifabutin, Rifampicin,

*Bold font indicates very strong inhibitor

Non steroidal anti-inflammatory drugs (NSAIDs)

Interaction can be due to drug displacement that are tightly bound, from its plasma protein binding site by NSAIDs. This may not occur with all NSAIDs but can be selective: oral hypoglycemics may not have clinically important interactions with NSAIDs but with drugs like phenylbutazone, aspirin and azaprozone, NSAIDs prolong their half-life while coumadin's half life is prolonged by phenylbutazone and azaprozone. Indomethacin,piroxicam, phenylbutazone and diclofenac decreases lithium clearance. NSAIDs displace methotrexate from its protein binding site but with

low doses of MTX, it is not clinically significant so it is utilized in patients with rheumatoid arthritis having normal renal function. Effects of NSAIDs are reduced blood flow, tubular excretion of drugs and renal prostaglandin production, also attenuation of anti-hypertensive drugs. Patients on indomethacin and triamterene have been reported with renal failure and hypercalcemia. Hence, under strict vigilance and scrutiny the safety profile of these drugs could be increased[38-40].

Antihistaminic drugs

These medications are not usually taken together. These medications may interact and cause very harmful effects.

Table 3: Interactions of Antihistamine drugs[41]

Antihistamines	Common Adverse Effects	Common Drug Interactions
Diphenhydramine	Anticholinergic effects, such as blurred vision, dry mouth, and urinary retention; dizziness; and drowsiness.	Alcohol, barbiturates, and other CNS depressants potentiate CNS effects.
Hydroxyzine	Anticholinergic effects, such as blurred vision, dry mouth, and urinary retention; dizziness; and drowsiness.	Alcohol, barbiturates, and other CNS depressants potentiate CNS effects.

Antidepressants

Research has concentrated on the relative effects of antidepressants on cytochrome P450 enzymes and, more recently, on drug transporters as potential mediators of clinically important pharmacokinetic DDIs. The most common, clinically relevant pharmacokinetic DDIs involve alteration in oxidative drug metabolism. Pharmacodynamic DDIs occur when the effects of a second drug quantitatively or qualitatively alter those of the first drug. Pharmacodynamic DDIs are not typically studied in vivo because of the potential for a serious adverse effect. All antidepressants can interact pharmacodynamically with certain other drugs[42-46].

Table 4: Some Important Drug Interactions with Antidepressants[47, 48]

Antidepressant dugs	Interacting Drugs	Possible Effects	Importance & Management
All	Alcohol	Increased CNS sedation.	Advice vigilance in early stages of treatment.
All	Benzodiazepine	Increased sedation possible. Fluoxetin and peroxetin may reduce metabolism of some benzodiazepine.	Warn that increased sedetion is possible.
All	Warfarin	Increased INR and increased bleeding risk due to antiplatelet effect.	Minor INR and advice patients to report signs of bleeding.
Fluoxetin &	Metoprolol &	Increasing β blocking	Monitor heart rate.

peroxetin	propranolol	effect, bradycardia.	Interaction not reported with citalopram.
All	Buspirone	Serotonin syndrome & lowering of seizure threshold theoretically possible.	Monitor concurrent use.
All	Antiepileptics	Selective serotonin reuptake inhibitors may lower the seizure threshold.	Unlikely to be a problem if epilepsy well controlled. Observe seizure frequently.
Fluoxetin	Antiepileptics, carbamazepine & phenytoin	Increased plasma conc. of carbamazepine & phenytoin with fluoxetine.	Monitor plasma conc. of carbamazepine & phenytoin. Adjust dose if necessary. No similar reports with peroxetin7 an interaction appears unlikely with citalopram.
All	NSAIDs including aspirin	Increased risk of GI bleeding.	Concurrent use not contraindicated but be aware of increased risk of bleeding specially in those with addition risk factors.
All	Monoamino oxidase inhibitor (MAOIs), including moclobemide	Hypertensive crisis.	Avoid concurrent use. Washout periods essential when switching. Refer to product prescribing inrotmation& reference texts.
Fluoxetine &peroxetine (possibly citalopram)	Clozapine, haloperidol, risperidone	Increased plasma concentration and antipsychotics.	Monitor for dose related adverde effect and reduce dose of anti psychotic if necessary.

Interactions between antiretrovirals and antitubercular drugs

In Tuberculosis and hiv prone areas, initially the antiretroviral drug regimes consist of efavirenz or nevirapine combined with NRTIs generally in fixed dosage form. Rifampin and NNRTIs undergo drug drug interaction which is of significance, also efavirenz based therapy is usually preferred for an initial antirertroviral therapyespecially in developed countries because of several advantages associated with it for example high potency, durability of efficacy in case of trials and it is used as a co-formulation with tenofovir and ematricitabine,given as once daily dosing[49-51]. USFDA approved rilpivirine, a second generation NNRTI, IN MAY 2011.so its available as fixed dose combination with tenofovir and emtricitabine .co-administration of rifampine and rilpivirine should be avoided as rifampine reduces AUC by 80 % and trough concentration by 89%.also some

predictions have been there that rifampin reduces the concentration of etravirine a second generation NNRTIs[52].

Antipsychotic drugs

As a consequence of individualized antipsychotic pharmacotherapy, many patients need more than a single drug, since they do not respond sufficiently to monotherapy. Other patients suffer from comorbid diseases and therefore require additional drugs from other pharmacological classes [53]. Drug combinations, however, can give rise to pharmacokinetic and/or pharmacodynamic drug-drug interactions. Evaluation of pharmacokinetic interactions with antipsychotic drugs must consider substrate, inhibitor, and inducer properties for the cytochrome P450 (CYP) isoenzymes of all combined drugs. For consideration of pharmacodynamic interactions, special attention must be given to effects on dopamine D(2), histamine H(1), and acetylcholine M(1) receptors and on cardiac potassium channels[54]. Additive pharmacological actions of combined drugs on these target structures can induce adverse reactions such as extrapyramidal symptoms, drowsiness, metabolic disturbances leading to weight gain and cardiac problems, cognitive impairment, delirium, or ventricular arrhythmia. Measuring plasma concentrations, i.e., therapeutic drug monitoring (TDM) is valuable to adjust antipsychotic medication when drug combinations contain inhibitors or inducers that alter plasma concentrations of the antipsychotic drugs. Amalgamating the broad knowledge on drug-drug interactions and using appropriately the option to monitor plasma concentrations in blood will help to apply complex combination therapies with antipsychotic drugs with maximal efficiency and safety[55].

Major antibiotic drug interactions

Table 5: Clinically Important Antibiotic Drug Interactions[56-60]

Antimicrobial	Other Agent(s)	Results of Interaction
Aminoglycosides	Neuromuscular blocking drugs Other nephrotoxins or ototoxins (e.g., cisplatin amphotericin B, ethacrynicacid, vancomycin, cyclosporine)	Increased neuromuscular blocade, Increased nephrotoxicity or ototoxicity.
	Penicillins	Inactivation of both drugs (a particular problem in renal failure and when obtainig drug levels).
Sulfonamides	Sufonylureas	Hypoglycemia
	Phenytoin	Increased serum concentration of phenytoin leading to toxicity.
	Procaine	Decreased sulfonamide effect.
	Oral anticoagulants (warfarin derivates)	Enhanced hypoprothrombinemia.

Chloramphenicol	Phenytoin, tolbutamine, ethanol	Increased serum concentration of other agents and enhanced pharmacologic effect or increased toxicity.
	Warfarin	Decreased warfarin metabolism and inhibition of vitamin K-producing gut bacteria, thus increasing prothrombin time.
Metronidazole (also cefamandole, moxalactam, cefoperazone) Macrolides, azalides	Ethanol (including ethanol-containing mediators)	Disulfiram-like reaction.
	Disulfiram	Psychosis.
	Theophylline	Increased serum theophylline concentration.
Amphotericine B	Curariform drugs	Increased curare-like effect.
Fluconazole	Phenytoin, warfarin	Inhibits metabolism of these drugs.
	Rifampin	Enhances metabolism of fluconazole.
Itraconazole	Astemizole, terfenadine	Cardiac arrhythmias.
	Phenytoin, warfarin	Inhibits metabolism of these drugs.
	Rifampin	Enhances metabolism of itraconazole.
Quinolones (norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, enoxacin)	Multivalent cations (antacids, iron, sucralfate, zinc)	Decreased absorption of quinolone.
Tetracyclines	Antacids, iron, calcium	Inhibit intestinal absorption of tetracycline.
Penicilins and cephalosporins	Uricosuric agents (probenecid, high-dose aspirin, etc.)	Block excretion of β lactams, causing higher serum levels.
	Cooper reduction test for Glycosuria (Clinitest tablets)	False-positive test for glycosuria (not seen with glucose oxidase method).
	Ethanol	Disulfiram reaction.
Isoniazid	Phenytoin	Increased serum concentrations of both.
	Warfarin	Increased risk of toxicity by decreased drug metabolism.

Sedative-Hypnotic and Anxiolytic Drugs[61, 62]

If a patient has a history of depression, or liver, kidney, and respiratory disease, it is advisable to communicate this to the treating physician in order to be certain that commencing treatment with hypnotics is safe.

Table 8: Drug Interactions of Sedative-Hypnotic and Anxiolytic Drugs

Drug	Common Adverse Effects	Common Drug Interactions
Benzodiazepines		
Alprazolam	Arrhythmia, CNS depression, drug dependence, hypotension, and mild	Alcohol and other CNS depressants potentiate effects.

	respiratory depression.	Fluoxetine and fluvoxamine increase serum levels and effects
Chlordiazepoxide	Arrhythmia, CNS depression, drug dependence, hypotension, and mild respiratory depression.	Alcohol and other CNS depressants potentiate effects. Cimetidine increases and rifampin decreases serum levels
Clonazepum	Arrhythmia, CNS depression, drug dependence, hypotension, and mild respiratory depression.	Alcohol and other CNS depressants potentiate effects. Cimetidine increases and rifampin decreases serum levels
Barbiturates		
Amobarbital	CNS depression, drug dependence, and respiratory depression.	Induces cytochrome P450 enzymes and increases metabolism of many drugs. Potentiates effects of other CNS depressants.
Pentobarbital	CNS depression, drug dependence, and respiratory depression.	Induces cytochrome P450 enzymes and increases metabolism of many drugs. Potentiates effects of other CNS depressants.
Other Sedative-Hypnotic Drugs		
Zolpidem	Dizziness, drowsiness, and headache.	Potentiation by alcohol and other CNS depressants.
Zaleplon	Dizziness, drowsiness, and headache.	Potentiation by alcohol and other CNS depressants.
Nonsedating Anxiolytic Drugs		
Buspirone	Dizziness, headache, and nervousness.	None
Propranolol	Bradycardia, bronchoconstriction, depression, fatigue, hypersensitivity, hypotension, impaired glycogenolysis, and vivid dreams.	Cardiac depression increased by calcium channel blockers.

Anticancer Drugs

The term 'drug interaction' is most often used to describe drug-drug interactions, but there are various substances and/or factors that can alter the pharmacokinetics and/or pharmacodynamics of medications. These include formulation excipients and environmental factors (such as cigarette smoking)[63, 64]. To exert a therapeutic effect a pharmacological agent must reach its target. Most antineoplastic agents are given intravenously and, therefore, factors that influence absorption have little effect on their pharmacokinetics. However, there has been increasing interest in the oral delivery of anticancer agents in chronic therapy, for patient convenience and ease of administration. for chronic myeloid leukemia (CML) and gastrointestinal tumours drug of choice could be Imatinib (oral administration).there are chances of interactions of drugs with food on oral

administration which can alter the bioavailability so oral delivery is a subject of concern anticancer agents which are delivered orally acts a prodrug, which further requires metabolic activation for cytotoxic activity and which is possible by first pass effect in GI tract / liver before its arrival to systemic circulation. some anticancer agents for treatment of solid tumours in case of breast ,colorectal ,ovarian, prostrate, lung and testicular cancer are capecitabine, altretamine, etoposide phosphate, and estramustine phosphate sodium[65, 66]. Therefore, factors that alter the absorption of these medications can have profound effects on their pharmacokinetics. A decrease in the rate and extent of absorption is noted when estramustine phosphate sodium is given with food or milk, and bioavailability has been reported to decrease by 36% and 63%, respectively[67]. Therefore, it is recommended that estramustine phosphate sodium be taken with water 1 hour before or 2 hours after a meal[68]. By contrast, food has been shown to have only a minor effect on the pharmacokinetics of fluorouracil (5-FU)[69]. The rate of absorption of capecitabine (a 5-FU prodrug) is decreased in a fed state, which results in an increase in hepatic first-pass metabolism, which in turn reduces the extent of systemic absorption of the prodrug. However, a greater effect is seen on the area under the concentration-time curve (AUC) of capecitabine as compared with 5'-deoxy-5'-fluorouridine (5'-DFUR), the precursor to the pharmacologically active compound 5-FU. So, the change in AUC of capecitabine is probably not clinically significant, as capecitabine itself is not the active compound. At present, it is recommended that capecitabine be taken with food, as this was the procedure that was used in the pivotal clinical trials[70]. Potential drug interactions between chemotherapy agents and anti-emetics have been extensively evaluated. Perhaps the most commonly used class of anti-emetics are serotonin antagonists. There are many of these compounds on the market, all of which have similar pharmacodynamic effects but have different pharmacokinetic properties. Only some of these agents inhibit the metabolism of a CYP enzyme. For example, granisetron does not inhibit CYP activity[71], whereas ondansetron has been shown to inhibit CYP1A1, CYP1A2, CYP2D6, CYP3A4 and CYP3A5in vitro[72]. Potential CYP-mediated pharmacokinetic interactions that reduce systemic exposure to the antineoplastic agent have been reported between ondansetron and both cisplatin[73] and cyclophosphamide[74]. However, the clinical significance of these interactions is unclear. Concomitant administration of a serotonin antagonist with a highly anti-emetic chemotherapy agent such as cisplatin and cyclophosphamide is the standard care[75], and so far no untoward effects have been reported.

Combating Drug Interactions

On the part of the prescriber, awareness and knowledge of possible and clinically manifesting drug interactions is the most important key factor involved in prevention of drug interactions. The roots

of this awareness emerge from the clear communication with the patient and meticulous history taking. The physician needs to know all the medications that the patient is receiving in order to understand, prevent or manage the possible drug interactions. This would include the medications prescribed by various prescribers as well as over-the-counter and herbal medications. To reduce the confusion, it is worthwhile to encourage the patients to prepare and bring the whole list of medications with them to a consultation. It is equally important to know the time and frequency of administration of various medications. It is worthwhile to know if without the knowledge of the doctor the patient stops or starts any of the medications or adjusts their dosages. One needs to inquire in detail regarding the intake of foods, alcohols and beverages. Role of clear communication with patients and with primary care clinician is important[76]. In addition, history taking also needs to include past history of major illnesses and interventions, allergies, illicit drug use and any known genetic factors. As far as awareness of possible drug interactions, the prescriber should know about serious and clinically manifesting adverse drug interactions, potentially interacting drug pairs, patient-related and drug-specific factors predisposing to drug interactions, and the substrate and precipitant drugs commonly involved in drug interactions. With all the due awareness of possibility of a potential drug interaction, the prescriber should be able to recognise it and then plan the appropriate action. This can minimise the risk of harm due to a drug interaction[77]. Appropriate measures are needed to avoid or minimise the impact of a drug interaction. These measures may include adjusting dose, route, order or sequence of administration or the spacing between the administration of interacting drugs. The measures also include anticipating the onset and peak effect of interaction and monitoring the patient at all times[78]. To minimise the risk of drug interaction, sometimes the physician may be able to simplify the drug regimen, by using one drug that serves two purposes or by reducing the number of times a drug must be taken[79]. At specific times, one of the precipitant drugs may need discontinuation and/or change in modality of an intervention may be required. A classic example is that of changing the method of contraception or delaying the decision to conceive, when a drug is absolutely necessary to serve the primary purpose in a particular illness (such as an anti-tuberculosis drug like rifampin or an antiepileptic agent such as phenytoin or carbamazepine or phenobarbitone), and is known to lead to failure of contraception. Awareness and knowledge of drug interactions is helpful in prevention of adverse events as well as for appropriate management of an illness. Further, pharmacovigilance measures involve anticipation of expected, predictable and highly predictable interactions in order to closely monitor the adverse event in case it happens[80].

How to Avoid Unwanted Drug Interactions

A full drug history including over the counter drugs and herbal products is required for drug interactions in clinical practice. Clinical effects of the drugs gives a clear picture of pharmacodynamic drug-drug interactions. A good knowledge in pharmacological field can make it easier; the key to it would be prescribing a few drugs but having a deep knowledge of all the drugs. Pharmacokinetic drug-drug interaction are difficult to predict as it cannot be interpreted from the clinical effects. Significant drug-drug interaction in clinical practice can be managed by five rules[81]:

a) Drugs can be categorized for differential diagnosis if any interaction between drugs have already been observed in patients.
b) Patient physiology and clear understanding of pharmacological actions of drug can predict pharmacodynamic drug-drug interaction.
c) Narrow therapeutic index drugs can be predicted to have pharmacokinetic drug-drug interaction.
d) Few drugs are perpetrators of pharmacokinetic drug-drug interaction
e) During prescription the decision to stop or start a drug can cause drug interaction.
f) After prescription, keeping a check on symptoms, biomarkers of effect and drug concentration can help in identification of drug interaction along with those monitoring patients for drug toxicity or loss of efficacy is a part of patient care.

CONCLUSION

Application of concepts involved in clinical pharmacology and good clinical care, most significant of drug interactions can be identified. changing drugs should be under strict scrutiny and vigilance of clinicians so that identification of drug interactions before they cause any potential harm can be done. since drug-drug interaction contributed at a significant level to adverse drug reactions so knowledge of few drugs and a deep knowledge of all the pharmacological actions of the drugs can prevent adverse reactions on a large scale. As part of preapproval risk assessment, the CDER has issued various guidance documents addressing study design, data analysis issues in the evaluation of drug interactions of new molecular entities (NMEs), and recommendations on drug labelling. An understanding of the clearance pathways of an NME and its modulating effects of CYP enzymes and certain transporters is essential in predicting human drug interactions and understanding possible mechanisms of these interactions. With continued improvement in our understanding of the mechanisms of interactions and contributions of additional patient factors

(e.g., genetics, gender), the risks associated with these interactions can be better predicted, assessed, and managed to reduce the frequency of clinically significant adverse drug reactions.

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