Drug interaction and its implication in clinical practice and personalized medicine

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ABSTRACT

In personalized medicine, the appropriate drugs for an individual patient are selected based on the patient’s medical history, diagnostic testing, and genetic information for the purpose of minimizing drug interactions (DIs), side effects, and adverse drug reactions (ADRs) and to obtain the maximum therapeutic benefit. The DI is one of the major problems of pharmacotherapy, which perhaps leads to adverse outcome or therapeutic failure if not properly addressed. In clinical practice, patient safety is likely to improve through the identification of frequently occurring DIs by pharmacist and notifying the other members of the health-care team. Recently, a software was introduced, which detects DIs with good precision; however, this software requires a constant update. Health-care professionals require adequate knowledge and skills on how to identify and avoid DIs to enable them complement the software assessment. Basically, DIs include drug–drug, drug–food, drug–herbal, and drug–disease interactions. These possibilities can be identified from chemical properties, pharmacokinetics, and pharmacodynamics of the drug, patient medical history, concomitant disease, or organ failure. Focusing on DIs will help to reduce drug-related problems, advance the evidence-based medicine, and improve the level of patient satisfaction. Adequate knowledge of drug DIs will enable the health-care professionals to individualize the patient treatment in order to get maximum therapeutic benefit. This script is aimed at describing the various classes of DIs, their causes, and their implications in clinical practice and personalized medicine.

KEY WORDS: Drug Interactions; Pharmacokinetics; Food; Herbal; Disease

INTRODUCTION

Drugs, apart from their ability to treat patients successfully, have the potential to cause harm. Several factors were identified to be responsible for the harmful effects caused by drugs. The drug overdose, drug interactions (DIs), self-medication, and medication error significantly contribute to adverse drug reactions (ADRs).[1–3] Basically, DIs cause altered pharmacological response leading to toxicity or therapeutic failure.[4,5] These processes are considered preventable and need intervention by improvement in diagnosing and prescribing skill.[5] Food, nutritional supplements, excipients, herbal medicine, concomitant disease, medication, and environmental factors are the contributors of DIs.[5,6] There is a potential possibility of harmful effects owing to DIs; however, they may produce some beneficial effects or no effect at all. Several investigations have shown that 10%–20% of the DIs have fatal consequences and are responsible for the patients’ hospitalization.[5,7] Elderly persons, pregnant women, children, and neonates are the most vulnerable group.[1–2] Polypharmacy and organ failure may potentiate DIs.[1,2] Because of the variation in the nature of our patients in terms of the food they take, herbal medicine, comorbid disease conditions, and the presence of other medical conditions, individualization of patient-treatment is indispensable.

CLASSIFICATION OF DRUG INTERACTIONS

According to professional guidelines, DIs are divided based on their nature and duration.[6]
1. Insignificant effect or no inconvenience: It refers to the DIs in which no harmful effect is observed.
2. Short-lived: This type of interaction causes inconvenience that lasts for up to 24–48 h but leave no residual symptoms.
3. Long-lived: This produces a harmful effect that lasts between 48 h and 168 h with no residual damage at the end.
4. Long-lived: This causes inconvenience for more than 168 h with residual symptoms or deformity.
5. Treatment failure: This leads to failure of life-saving therapy or increase risk of pregnancy in women taking contraceptives and causes hypertension, myocardial infarction, cardiac arrhythmia, and rhabdomyolysis.
6. Death and life-threatening effects: It results in Tosade de pointes, serotonin syndrome, ventricular arrhythmia, or hyperpyrexia.

**NATURE OF DRUG INTERACTIONS**

**Pharmacokinetics Interaction**

It occurs when one drug changes the concentration of another drug taken concurrently with clinical consequences. It occurs by altering processes such as drug bioavailability, distribution, metabolism, and excretion.\(^{[4,5,9]}\)

**Pharmacodynamics Interaction**

It occurs when two or more drugs with opposite or additive effects are coadministered. This is common with drugs that act in the central nervous system.\(^{[4,5,9]}\) The entire process may occur by additive effect, synergistic, or antagonistic actions of individual drugs.

**MECHANISM OF DRUG INTERACTION**

The DIs occur via three possible mechanisms listed below: \(^{[8,9]}\)

1. Direct inhibition or induction of metabolic enzymes.
2. Indirectly by inhibition or induction of transcription factors that regulate enzymes.
3. By inhibition or induction of drug transporters.

**Polypharmacy**

It involves the use of many drugs at the same time for patient treatment than clinically required. It is common in elderly patients with comorbid disease conditions. Patients with hypertension, diabetes, and other chronic diseases are more likely to experience polypharmacy.\(^{[9,10]}\) Polypharmacy may cause ADRs owing to the drug additive effect, synergism, duplication, DIs, discontinuation of treatment, and physiological antagonism. It was reported that patients aged above 65 years use an average of two to six prescribed drugs and 1 to 3.4 nonprescribed drugs.\(^{[11]}\) Moreover, patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids at the same time showed 15 times risk of developing peptic ulcer than patients not taking either of the two drugs.\(^{[11]}\) Prescription cascade may arise when a physician could not diagnose ADRs, regarding it as a symptom of disease that warranted an additional medication leading to more ADRs.\(^{[11]}\)

**Incidence of Drug Interactions**

The incidence of DIs is believed to increase with polypharmacy. The incidence of DIs is 40% in patients taking five drugs and perhaps up to 80% in patients taking seven drugs.\(^{[1,7,10]}\) The female gender was established to be more prone to DIs owing to their frequent hospital visits.\(^{[11,12]}\) In a developed country such as Switzerland, the incidence of DIs was 23%.\(^{[7]}\) A Dutch study among pharmacies showed that 28% of the prescriptions revealed DIs.\(^{[9]}\) Similarly, in Romania, 48% of elderly patients experienced the consequences of DIs, whereas 34% was reported from the rest of the population.\(^{[7]}\) The prevalence of DIs was estimated as the ratio of drug–drug interactions (DDIs) per patient, which was from 0.62 to 1.05 in different European countries.\(^{[7]}\) Dutch University Hospital published a report on the commonly experienced side effects due to DDIs, which include the increased risk of bleeding (22%), hypotension (15%), nephrotoxicity (13%), and electrolyte imbalance (11%).\(^{[6]}\)

**The Role of Cytochrome P-450**

Cytochrome P-450 (CYP) is the family of isoenzymes that carry out metabolism of drugs and other substances in the body. Drug biotransformation via this system of enzyme is one of the major routes through which potential DIs take place leading to drug toxicities, ADRs, or therapeutic failure.\(^{[4,8,12,13]}\) Six major classes of CYP isoenzymes that play a vital role in drug biotransformation are CYP 1A2, CYP 2C9, CYP 2C6, CYP 2E1, and CYP 3A4.\(^{[4,8,9,12,13]}\) Isoenzyme CYP 3A4 is found more commonly in the liver, but drug metabolism also occurs in gastrointestinal tract (GIT), lungs, skin, and kidney. CYP 3A4 is located in the smooth endoplasmic reticulum. It is responsible for drug activation and inactivation and extensive first pass metabolism.\(^{[4,9,12,13]}\) DIs occurs possibly via enzyme inhibition, induction, and other possible means. Enzyme inducer increases the metabolism of competing drugs; consequently, more of the drug will be biotransformed leading to a reduced efficacy or therapeutic failure. However, if the drug has an active metabolite, enzyme induction will yield more of the active metabolite causing drug toxicity. Example of this scenario is an alcoholic patient taking paracetamol.\(^{[4,8,9,13]}\) However, if the drug is a produg, inhibition of its metabolism will reduce its conversion to active drug leading to a decrease in the pharmacological action.\(^{[4,9,13]}\)

Variation may exist in the individual’s ability to metabolize drugs. This is perhaps owing to genetic polymorphism, disease, age, and possibly gender difference. Genetic polymorphism is common with CYP 2C19 and CYP 2D6 isoenzymes.\(^{[13]}\) Patients with intact CYP 2C19 and CYP 2D6 isoenzymes metabolize the drug normally and are considered as extensive metabolizers. On the other hand,
patients lacking these isoenzymes are called poor metabolizers. Disease condition affecting the vital organs such as liver damage, decrease the drug biotransformation significantly. Similarly, congestive heart failure due to decrease in blood flow significantly decrease the drug metabolism. Elderly patients reveal decreased CYP-450 mono-oxygenase enzyme, decreased blood flow to the liver; decreased liver size and, consequently, metabolic activity.

In addition, neonate has a decreased rate of drug metabolism owing to the under development of CYP 450 enzymes in the liver.

**Drug–Drug Interaction**

**Introduction**

DDIs take place when two or more drugs administered concurrently, produce an effect that is not consistent with the principal pharmacological action. DIs between potassium supplement and potassium sparing diuretic may cause life-threatening hyperkalemia. Similarly, patients treated with sulfonylureas while taking sulfonamide antibiotic are at risk of developing hypoglycemia. This is owing to the inhibition of the metabolic enzyme CYP 2C9 by sulfonylureas. Moreover, a patient taking digoxin and clarithromycin concurrently is at risk of digoxin toxicity, as a result of the inhibition of 31 digoxin efflux pump. Prescription of potassium-sparing diuretics and angiotensin-converting enzyme inhibitors (ACEIs) may lead to serious hyperkalemia caused by both drugs. Concurrent use of ACEIs with thiazide diuretics lead to excessive diuresis and hypotension. A similar interaction is seen in the combination of β-adrenergic blockers with dihydropyridine calcium channel blockers.

Chlorphenamine also inhibits isoenzyme CYP 2D6 responsible for the biotransformation of dextromethorphan; when the two drugs are combined together, the patient is likely to experience serotonin syndrome. Administration of quinidine, which is an inhibitor of CYP 2D6 isoenzyme responsible for cancerous cell DNA synthesis causing cell death. This is considered as beneficial DDI and is commonly employed in the treatment of colorectal cancer.

**Anticancer Drugs Interaction**

Anticancer agents are highly toxic and yield fatal side effects; hence, they require the attention of health-care professionals. DIs by this class of drugs are very common owing to their narrow therapeutic index. Strong association exists between the therapeutic action of these drugs on cancer cells and toxicity on normal cells. Some of the cancer drugs are metabolized by polymorphic enzyme, and their renal clearance may cause nephrotoxicity. Patients taking 6-mercaptopurine with xanthine oxidase inhibitors may experience cellular toxicity, as these drugs inhibit the metabolism of 6-mercaptopurine by the enzyme thiopurine methyltransferase, raising its plasma concentration.

In addition, coadministration of 5-flourouracil and folinic acid will potentiate the inhibition of thymidylate synthase responsible for cancerous cell DNA synthesis causing cell death. This is considered as beneficial DDI and is commonly employed in the treatment of colorectal cancer.

Treatment with teniposide and etoposide in patients taking anticonvulsants may experience an increase in the renal clearance of the first two drugs leading to therapeutic failure. It is imperative to note that there is an acceptable level of toxicity to cancer drugs above which patients or nurses should raise an alarm.

Cancer treatment with 5-flourouracil in patients taking anticoagulant warfarin may cause increase in bleeding time due to inhibition of the metabolic enzyme. Probenecid inhibits methotrexate excretion when combined together leading to neutropenia and systemic toxic effects even at low dose. In oncology, the sequence at which drugs are administered is important in reducing drug toxicity; patients treated with paclitaxel, followed by cisplatin, experience a profound decrease in the generation of platinum adducts in their DNA. Platinum adducts are believed to be the major cause of toxicity in cancer therapy. Patients treated in this sequence are likely to experience fewer side effects than those taking cisplatin before paclitaxel.

**Other Forms of Drug-Drug Interactions**

Some categories of DDIs exist that do not affect the drug metabolizing enzymes. Changes in gastric pH by one drug may significantly alter the bioavailability of the other drugs taken concomitantly. A large number of drugs administered orally require a pH between 2.5 and 3.0 for them to be absorbed successfully. The absorption of drugs such as antacids, PPIs, anticholinergics, and H2 antagonists is impaired when the pH is raised above this level. However, these drugs themselves raise the gastric pH leading to the decrease in absorption of cefpodoxime, while increasing the absorption of β-blockers and tolbutamide. Drugs such as ketoconazole, fluconazole, methotrexate, clopidogrel, paroxetine, and diazepam require an acidic medium for their optimal absorption. The intake of these drugs at the same time with PPIs, antacids, and anticholinergic drugs may reduce their bioavailability. However, administering them together with pentagastrin, which decrease gastric pH, is likely to increase their absorption.

Antacids are also known to form complexes with drugs such as tetracyclines, fluoroquinones, and penicillins, causing a decrease in their absorption. In addition, cholestyramine binds to acidic drugs such as warfarin, furosemide, phenytoin, aspirin, and sulfonamides to form complexes that cause reduced
bioavailability.\[9\] Motility impairment or drug contact time with the GIT walls are additional factors in drug absorption. Metoclopramide and cisapride reduce slow release drugs contact time with the GIT, and hence, decrease in their absorption. At the same time, metoclopramide may accelerate gastric emptying time of digoxin and theophylline, resulting in reduction of their bioavailability. An exactly opposite effect occurs with tetracycline, paracetamol, levodopa, and aspirin.\[9]\] Diclofenac displaces warfarin from its binding site and raises the plasma concentration of free warfarin, which leads to toxicity.\[9\]

Prevention of Drug–Drug Interactions

DDIs can be predicted and avoided through the knowledge of their mechanism; by identifying the enzymes responsible for the particular drug metabolism; and by identifying the enzymes’ transporters and modulators. This is followed by the use of clinical expertise to determine whether inhibition or induction of these factors will lead to clinically significant DI or not.\[9\]

This analogy can be demonstrated by the combination of phenytoin and gefitinib. Phenytoin is an enzyme inducer of CYP 3A4 isoenzyme responsible for the metabolism of gefitinib; induction of this enzyme by phenytoin will lead to an increase in the metabolism of gefitinib, resulting in reduced plasma concentration and pharmacological action.\[1\] Large percentages of DDIs were believed to occur owing to genetic polymorphism.\[9\]

For a drug combination to cause clinically significant DDIs, the interacting drug (perpetrator drug) should be able to increase or decrease the biotransformation of the other drug (object drug) by twofold. It may be necessary to find out whether the object drug is an active drug or prodrug and whether it is metabolized to an active or inactive metabolite.\[4,8,9\] DDIs can be prevented or minimized through dosage adjustment and spacing the time between intakes of the interacting drugs.\[4,7,9,10,15\] It is very important for a physician to bear in mind that the possibility of DDIs in treating patients with chronic and comorbid disease condition is very high. Moreover, elderly patients with cardiovascular or alimentary canal disease are more prone to DDIs because of polypharmacy.\[4,7,9,15,17\]

One of the well-known DDIs is the concomitant use of warfarin and aspirin or clopidogrel, which prolonged the clotting time and increased risk of bleeding. Another example is clopidogrel and PPIs, which cause the risk of reinfarction. PPIs competitively inhibit CYP 2C19 and CYP 3A4 enzymes responsible for the biotransformation of clopidogrel to an active drug, leading to loss of antiplatelet activity.\[4,9,15\]

A careful identification of DDI will enable the prescriber to individualize patients therapy.

**Drug–Herbal Interactions**

**Introduction**

Herbal medicines include the use of whole plants, plant parts, an extract, or mixture preparations in the treatment or prevention of various diseases. Herbal medicine is believed to have existed 100 years before the advent of orthodox medicine.\[10,19\] A large number of people believed that herbal medicine is a natural product and is almost free from ADRs. However, a majority of herbal preparations contain up to 150 active constituents.\[18–21\] Herbal medicine may interact with the orthodox medicine or other herbal preparations causing either an increase or decrease in their pharmacological action or toxicity. Researchers have shown that 50% of patients taking herbal medicine are cancer patients owing to the narrow therapeutic index of cancer medicine.\[18–21\]

A survey reported that 72% of patients taking herbal medicine do not disclose it to their physician.\[18,20–22\] Furthermore, 15% of physicians do not ask their patient about any herbal medicine they are taking, and 40% of the patients in the United States admitted that they combined herbal with orthodox medicine.\[18–20\] There was an evidence that 30% of the population in Washington use herbal preparations with little or no safety information. Consequently, in the United States, up to about 8,000 to 16,000 ADRs owing to herbal medicine were recorded annually.\[20,22\] The drug–herbal interaction (DHI) is of clinical importance; the major drawback in this area is the incidence of underreporting.\[19,23\]

**Mechanism of Drug–Herbal Interactions**

The DHIs occur via both pharmacokinetics and pharmacodynamics mechanisms. Specifically, herbal medicine commonly interacts by interfering with the pharmacokinetics parameters.\[18,19\]

**Mode of Interactions of Common Herbal Plants**

**St. John’s wort (Hypericum perforatum):** It is a popular plant used as an antidepressant. It contains the active compound hypericin that inhibits amine reuptake. Concomitant use of this plant with other antidepressant drugs will produce serotonin syndrome.\[18,19,21,22,24,25\] St. John’s wort is a powerful inducer of drug metabolic enzymes, especially CYP 3A4 and CYP 2C19; as such, it reduces the plasma concentration of warfarin, cyclosporine, benzodiazepines, and anticonvulsant and oral contraceptives. Furthermore, it interacts with tetracyclines, PPIs, and sulfonamides to cause photosensitivity.\[18,19,21,22,24,25\]

During HIV treatment, this plant induces CYP 3A4 that is responsible for the metabolism of protease inhibitors, leading to reduced plasma concentration, treatment failure, and drug resistance. Transplant patient taking immunosuppressant cyclosporine exhibited DHIs. St. John’s wort induces multidrug transporter P-glycoprotein in laboratory rat; hence, it increases the absorption of cyclosporine.\[18,19,21,22,26\] Similar therapeutic failure was observed if the same plant was combined with verapamil or statins, which yield a poor control of blood pressure and cholesterol levels. However, St. John’s wort preparations inhibit metabolism of tamoxifen to a greater extent, while inhibition of irinotecan metabolism is to a lesser extent.\[20,21,24,25\] Physicians should strongly advise their patients to ensure giving a 2-week washout period for St John’s wort before taking standard treatment.\[19\]
Ginger (Zingiber officinale): This herb is used as an anticoagulant. Its active constituent parthenolide inhibits platelets aggregation via inhibition of serotonin release with no bleeding side effect recorded.[19] Inhibition of platelets aggregation also involves the release of collagen fibers, arachidonic acid, epinephrine, and adenosine. Drugs acting via this mechanism are likely to interact with ginger.[18] Ginger preparations also inhibit the metabolism of tamoxifen to a greater extent and irinotecan to the lesser extent.[20,21,24,25]

Garlic (Allium sativum): This is popularly used as antiplatelets and antihypertensives and in the treatment of hyperlipidemia. Garlic is an active compound in garlic and is directly implicated in the induction of CYP 3A4, CYP 2C9, and CYP 2C19 isoenzymes. It is also believed to inhibit the transporter P-glycoprotein.[18–20,22,26] The coadministration of protease inhibitor and garlic will lead to a rapid metabolism of saquinavir, fall in blood concentration, and therapeutic failure. The intake of garlic by patients treated with warfarin will produce a synergetic effect causing bleeding disorder.[18–20,26]

Ginseng (Panax ginseng): This plant is used as an antiplatelet. The crude extract of this plant inhibits metabolic isoenzyme CYP 2E1 in mouse and human. Also, the plant active constituent, ginsenoside, causes a weak inhibition of CYP 3A4, 2D6, and 2C9 isoenzymes. Another compound, ginsenodiol, exerts an opposite effect by inducing CYP 2C9 and CYP 3A4 isoenzymes.[18–20,25,26] In general, ginseng causes the induction of warfarin metabolism and loss of therapeutic activity; it also stimulates cytokines, and therefore, it may induce mania when combined with antipsychotics. Case reports indicated that it raises the serum concentration of digoxin and causes toxicity.[18,26]

Ginko (Ginkgo biloba): This herbal medicine is used in the treatment of dementia. Extract of this plant is believed to inhibit metabolic isoenzyme CYP 3A4 leading to the decrease in the metabolism of diltiazem. On the other hand, it induces CYP 2B.[18,19,25] An active constituent, ginkolic acid, is found to inhibit CYP 1A2, 2C9, 2C19, and 3A4 isoenzymes.[18,19,25] G. biloba inhibits the metabolism of warfarin and aspirin and causes bleeding, and it impairs the blood pressure control when taken with a diuretic.[18,19,26]

Aloe vera (Aloe barbadensis): This herb is taken for its antidiabetic and anticoagulant actions. It is also used to treat skin infection. It precipitates anticoagulant action when used at the same time with warfarin. In addition, it should not be used concurrently with antidiabetics and laxatives, as it may cause an additive effect leading to toxicity.[18,20,25] Aloe vera causes potassium loss; intake of it at the same time with digoxin and thiazide diuretics will precipitate arrhythmias.[18,20,25]

Liquorice (Glycyrrhiza glabra): This plant is common in Chinese herbal medicine. It consists of the active constituent glycyrrhizin, which inhibits enzymes such as 5β-reductase, 5α-reductase, and 11β-dehydrogenase. Inhibition of these enzymes leads to the inhibition of corticosteroids biotransformation causing toxicity.[18,20,24] Liquorice also causes salt and water retention; hence, it should not be combined with diuretics.[14] If a physician is aware of herbal medicine taken by his patients, he can counsel them on how to avoid DFI or select their medication individually.

**Drug–Food Interactions**

Drug–food interactions (DFIs) pose many challenges during drug treatment. This is because patients are used to a particular food over a long period, which may not be friendly with their disease condition or the drug they are taking. In addition, habitual foods of patients are not usually recorded in their hospital file, and it is often difficult to predict which food a patient is likely to take next.[27] Although DFI is less dangerous, it is often difficult to address and, at times, may lead to hospitalization. Underreporting is one of the major problems of DFIs.[23] The main ways through which DFIs occur is by the alteration of pharmacokinetic variables.[14,23,27,28] Changes normally occur in the body in response to food intake such as gastric acid secretion, GIT motility, and modification of transporter P-glycoprotein or chelation by food. DFIs may lead to synergistic, additive, or antagonistic drug effects.[20,29] It is important to note that, apart from the disadvantages of DFIs, they can also be used to modify the drug bioavailability and reduce the adverse effects.[27] However, food containing tyramine when taken by a depressed patient treated with tricyclic antidepressant or serotonin reuptake inhibitors will produce supra concentration of serotonin. This will cause hyperactivity, hypertensive crisis, and perhaps stroke.[27] These patients should avoid tyramine containing food such as chocolate, pasteurized milk, cheese, concentrated yeast extract, fermented cabbage, red wine, and so on.[23,27] Ciprofloxacin, tetracycline, or sodium fluoride if taken with milk, the metals in the milk will form a complex with these drugs and impair their absorption. However, artemisinin classes of drugs are better absorbed when taken with milk, and absorption of griseofulvin is enhanced by fatty foods.[23,27,29]

Pharmacological action of drugs such as benzodiazepines, opiates, phenobarbital, and antihistamine are believed to increase when taken with alcoholic drinks. In addition, chronic alcohol abuse reduces the efficacy of phenytoin but increases the toxicity of methotrexate and acetaminophen.[27,29] Foods containing high amount of vitamin K when taken at the same time with warfarin will activate clotting factors, thereby decreasing warfarin efficacy.[23,27] Grape fruit juice (GFJ) is a powerful enzyme inhibitor, especially CYP 3A4, and P-glycoprotein transporter; it may inhibit the metabolism of many drugs to a greater extent when taken together. It raises the concentration of cyclosporine, felodipine, and midazolam causing toxicity.[28,29] GFJ inhibits the metabolism of most psychotropic drugs, and possibly, anticonvulsant drugs and causes toxicity. It also inhibits esterase enzyme; hence, it is not to be used with statins and calcium channel blockers.[28,29] Warfarin when taken concurrently with high protein diet may lose its activity owing to the increase in plasma protein binding and metabolism by CYP 450 enzymes.[29] It is, therefore, necessary to avoid GFJ 2 h before and 4 h after medication.[14,27]
Drugs such as isoniazid, sulfonylureas, PPIs, and glipizide should be taken on empty stomach to avoid DFIIs.[23,29] One of the advantages of DFIIs is that drugs that cause gastric irritation are better taken with food to reduce the GIT side effects. Methotrexate decreases the level of vitamin B and folic acid; intake of this drug with food containing these vitamins is advantageous.[14] Knowledge of the food taken by the patients will help the doctors in selecting their medications and personalize the treatment.

**Drug–Disease Interactions**

Drug–disease interactions (DDISs) are situations whereby a new drug treatment excavates the preexisting medical condition. It also implies the ability of a newly prescribed drug to cause side effects similar to one of the patients’ disease condition.[30] In the United States, 25% of patients in ambulatory care and 40% of hospitalized patients are at-risk of DDISs.[17] The prevalence of DDISs in the US was determined to be 15%–40%.[30] Several risk factors were identified to be strongly associated with DDISs including old age, children and neonate, female gender, psychiatric comorbidities, Hispanic race, and primary health-care visit. Another study found that white people showed a higher risk of DDISs than the African Americans.[14,30] The cases of DDISs identified to have an adverse outcome include treatment with first-generation Ca²⁺ channel blocker in patient with systolic heart failure; use of α-blockers in syncope; and use of NSAIDs in peptic ulcer. Other important disease conditions that are excavated by the presence of another drug include liver disease, heart failure, dementia, chronic renal failure, and falls.[30] In addition, patients with other chronic disease such as diabetes, hypertension, and asthma should be closely monitored for the episode of DDISs. Patients with central nervous system disorders such as anxiety, schizophrenia, bipolar disorders, depression, alcohol dependence, and posttraumatic stress disorders are also at a high risk of developing DDISs.[30]

According to the theory of pain and inflammation, pain reduces the absorption of cardiovascular drugs and analgesics considerably. Acute pain after surgery impair the absorption of ibuprofen and naratriptan 5-hydroxytryptan inhibitors causing a decrease in the plasma concentration and pharmacological action.[31] The decrease in absorption was due to inhibition of vagus nerve by pain stimulus or trauma, which prolonged the gastric emptying time.[31] DDISs are strongly associated with type A (augmented) ADRs in elderly patients.[32] Cardiovascular drugs and NSAIDs were found to be the most common cause of hospital admission because of DDISs. The usual symptoms are hyper- or hypotension and gastrointestinal bleeding.[17] In addition, the most frequent interactions among the prescriptions studied involved the treatment with NSAIDs in hypertensive patients or patients with chronic heart failure and coadministration of ACE inhibitors and NSAIDs.[17] A full knowledge of underlying disease conditions of the patients will help to make their treatment personal.

**Conclusion**

The pharmacological action of a particular medicine may be exaggerated or become much lower than the expected outcome. This is perhaps due to the DDISs, DFIIs, DHIIs, or DDDISs, which could be accidental or owing to the lack of awareness by the health-care professionals. The final effects of the drug usually produced may add up from the nature of the interaction it was involved or it may produce entirely a new form of activity. Individual nature of patient, presence of comorbid disease, feeding habit, and environmental conditions play an important role in the treatment of the patients. Individualization of patient treatment will help to reduce the DIs and incidence of ADRs. In order to practice the most efficient evidence-based medicine and to provide health-care services needed in the 21st century, personalized medicine should be at the fore front of health-care providers’ agenda. Patient treatment is a service provided by health-care providers, paid by the patient, his relatives, or his government; therefore, customer satisfaction is a paramount issue. Because health-care service delivery is a division of responsibilities, pharmacists remain the best professionals entrusted with the aspect of pharmacotherapy and the success of health-care team can only be achieved if all health-care professionals are regarded as stake holders in their respective fields.

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