WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 3, 743-773. Research Article ISSN 2277– 7105

UNDERSTANDING ADVERSE DRUG REACTIONS AND DRUG ALLERGIES: PHARMACOVIGILANCE –URGENT NEED OF THE HOUR IN INDIA

Dr. Gohil Kashmira J.*

Director, Anand College of Pharmacy,
Sharda Group of Institutions (SGI) Agra- 282007. U.P. India.

Article Received on
26 Dec. 2016,
Revised on 16 Jan. 2017,
Accepted on 06 Feb. 2017
DOI: 10.20959/wjpr20173-7894

***Corresponding Author**
Prof Gohil Kashmira J.
Ph.D, M. Pharm
(Pharmacology),
Director/Dean,
Anand College of Pharmacy,
Sharda Group of Institutions
(SGI) Agra-282007, U.P.

ABSTRACT

Adverse drug reactions (ADR) and drug allergy are challenging and major cause of morbidity and mortality worldwide. Many hospital admissions are because of ADR and from hospitalized patients; many experience serious ADRs, complicating the situation and therapeutic drug courses. Epidemiologic data supports the existence of specific factors that increase the risk of general ADRs such as specific populations, age, female gender and pharmacogenetics and polymorphism. Complicating factors of drug reactions include the myriad clinical symptoms and multiple mechanisms of drug-host interaction, many of which are poorly understood. This review aspires to explain the details on types of various ADR, their mechanisms with examples and underlying causes. The treatment options are based on the types of ADR encountered. Reporting ADRs and their effective management are the urgent needs of the hour today.

KEYWORDS: Adverse drug reactions, drug allergy, drug interactions, types, mechanism, reporting, treatments, Pharmacovigilance in India.

INTRODUCTION

Adverse drug reactions (ADR) are one of the major health concerns in this era with the multiple drugs explosion in the market and inadvertent use of various drugs by public, over the globe. The problem came to public attention worldwide in terms of ‘thalidomide’ tragedy which was struck in 1956 in Europe, when many pregnant women have taken this drug for the symptom as simple as morning sickness and as a hazardous consequence, given births to

babies with loss of limbs and skeletal malformation, a condition known as 'phocomelia'.[1-3] India, with a Pharmaceutical market valued at 18 billion growing at 14% per annum and importer of 40% generic drugs worldwide, face this issue seriously.[4-5] More so, because India has emerged rapidly as an important hub for clinical trials and clinical research and also the fact that large number of drugs are produced and consumed in India making it a 4th largest producer in the pharmaceutical products in the world and supposed to outperform the global pharma industry.[6-7] Many factors raise the concerns with huge geographical base in India, with large number of population close to 1.2 billion and still increasing, different pattern of disease prevalence, ethnic variability, various cultures, different socio-economical pattern and the practice of using different alternative systems of medicine such as Ayurvedic, herbals, homeopathic and Unani etc., enormously increase the risk of exposure to various kinds of ADRs. What we need is a robust and standardized system of pharmacovigilance in the country to tackle the problem at hand.

Drugs are prescribed to produce desired therapeutic effects in the patients. But anything that produces an effect could be good as well as bad. Drugs as a general can produce good, bad or even neutral effects. There is no distinction between drug and a poison, as a matter of fact. A poison in a small quantity can work as a drug and a drug in excessive quantity can work as a poison. A drug minoxidil lowers blood pressure is a desired therapeutic effect of the drug, but when it produces hirsutism, or abnormal hair growth, it is a side effect. The same may be considered a good effect for the bald person. But the hepatotoxicity produced by the paracetamol is a bad reaction. A very bad reaction like this is called an adverse drug reaction.

ADR: the standard definitions[8-10]

ADR are the unwanted effects produced by the drug prescribed at normal therapeutic dose in human beings. It may produce unpleasant effects or even harmful effects necessitating the reduction in the dose or total withdrawal of the drug if necessary. Deliberate overdose or therapeutic failure of the drug is not considered as an ADR.

World health organization defines ADR as- "any noxious, unintended and undesired effects of a drug which occurs at the doses used in humans for prophylaxis diagnosis or therapy or modification of physiological function excluding failure to accomplish intended purpose".

Food and drug administration (FDA) in US defines ADR as- "any experience associated with the use of a drug whether or not considered drug related and includes any side effects, toxicity, sensitivity reaction or a significant failure of an expected pharmacological action".

There is a difference between side effect and ADR. While side effects are supposed to be known in advance and labeled on product as cautions, occurs at therapeutic dose prescribed and patients can be given precautionary steps and medications to counteract the same. While ADRs are hitherto unknown, may occur at any dose prescribed and require urgent medical interventions at hospital.

Incidence: according to various landmark surveys taken all over the world, ADR is one of the 10 leading causes of morbidity and mortality in the world.[11] Over 200 million people across the globe suffer from it. Over 1, 00,000 deaths reported annually and about 5-10% of hospitalized patients have serious ADR with mortality rate of 0.35, which are fatal in nature.[12] These all facts tremendously increase the total health care cost and thus overall economic burden on the country.[13] Moreover, in a country like India with a large biodiversity, large numbers of people are dependent upon plant and herbal based products as an alternative therapy, thinking that nature as safe. This is also one reason, the patients also do not report the herbal compounds even if they are taking them along with the allopathic medicine to their physicians. Contrary to the popular belief, that natural compound is safe; the same can have additional, synergistic or antagonistic effects with other allopathic or their counterparts and can have hazardous consequences.

Factors predisposing: here are numerous factors that predispose to ADR as listed below.

Age: Age is particularly an important factor**.** Both the extremes of the ages, pediatrics as well as geriatric populations are very susceptible to various kinds of ADR. Infants, especially premature neonates are susceptible to ADR.[14-16] The causes being, they have large amount of body water, premature hepatic drug metabolizing enzyme system, ineffective renal system, apart from the other facts that children are unable to express their response or concerns towards drugs they are taking and the fact that limited number of pediatric dosage forms are available in market. Neonates have immature renal tubular function, below the age of 8 weeks. So avoiding digoxin, aminoglycosides, ACE inhibitors, NSAIDs was advised.[17] As Physiologic hypoalbuminemia affects drug dosing, a great caution is recommended when dosing with high protein binding drugs such as NSAIDs in neonates.[18] Also, Neonates, have

low body fat; they are supposed to get affected by fat soluble drugs.[19] Increased anesthetic effects due to immature blood brain barrier in neonates 8 weeks of age was indicated.[20] Predisposition to hypotension and other complications were reported due to poor cardiac compliance.[21-22] Some well known example of ADR experienced in children are, dentification, ossification problems by tetracycline,[23] grey baby syndrome by cloramphenicol due to a lack of glucuronidation reactions occurring in the baby, thus leading to an accumulation of toxic chloramphenicol metabolites[24-25] and Reye's syndrome by aspirin, a potentially fatal syndrome with unknown causes that usually occurs in children who have had a recent viral infection, such as chickenpox or the flu.[26] It has numerous detrimental effects to many organs, especially the brain and liver, apart from causing low blood sugar. [27] Specific Efforts are needed to predict and prevent the occurrence of ADRs in children. [28] Likewise, for geriatric populations, ADRs are prevalent. [29-30] The causes for this fact are different but consequences are the same. The elderly people have small amount of body water and plasma protein concentration especially albumin, decreased efficiency of hepatic enzyme in liver and thus loss of ability to metabolized drugs or excrete drugs by kidney, attributed to age.[31-32] This will prolong the drug stay in body increasing the risk of ADR. [33] Apart from these, other concerning factors like concomitant diseases like hypertension, diabetes and other lifestyle diseases is also very prevalent in the elderly. So poly pharmacy because of that highly increases the chances of predisposing geriatric population to various kinds of drug interactions and ADR. Some classes of drugs increasing the risk in elderly towards ADR are, NSAIDS, antihypertensive, hypoglycemic, cardiotonics and anticoagulants. The utmost cautions need to be exercised while prescribing drugs in elderly. [34-35]

Gender: Gender does affects and plays a role in predisposing to ADR due to biological differences. Women have more chances of exposure to various ADR than men because of their lower bodyweight and organ size, more body fat, different gastric motility and lower glomerular filtration rate. These differences can affect the way the body deals with drugs by altering the pharmacokinetics and pharmacodynamics of the drugs including drug absorption, distribution, metabolism and elimination.

Several studies indicated the potential sex differences in the expression of hepatic drug metabolizing enzymes and reported that hepatic enzyme CYP3A4 is more active in females than males which lead to different effects on drug metabolism.[36-38] So, drugs metabolized by

this particular enzyme may exhibit lower activity in women. Variability in the frequency and severity of ADRs to antiretroviral drugs was also reported due to gender. [39] Pharmacodynamic variability due to gender is also reported. Chlorpromazine and fluspirilene were found to be more effective in women than in men for the same dosage and plasma concentration.[40] It was stated that the female gender is a risk factor for hepatotoxicity more than men.[41] Some examples of drugs at risk for causing diverse ADR are, various blood disorders by phenylbutazone, histaminoid reactions by neuromuscular drugs, quinidine like drugs and drugs working on GIT. The most striking differences between women and men were seen in a study about the incidence of ADRs caused by cardiovascular medications like low-ceiling diuretics, high-ceiling diuretics, cardiotonic glycosides and coronary vasodilators. [42] One study reported higher incidence of cough in females compared to males taking angiotensin converting enzyme inhibitors (ACEI).[43]

Pregnancy: The women related conditions such as pregnancy, menopause and menstruation may have profound drug effects and variable drug responses.[44] This is due to certain physiologic changes that occur during pregnancy which might affect drug pharmacokinetics and pharmacodynamics. In pregnancy, the total blood volume increases by 30–40% (1500–1800 ml), extravascular volume increase during the 2nd and 3rd trimester which leads to decreased plasma concentration of iron and some drugs, renal function improves with a renal plasma flow increment of 30% and GFR increases 50%, serum protein 1–1.5 lower; thus drugs excreted by kidney would have an increased rate of excretion, cardiovascular changes as noted by an increase in cardiac output of about 32% due to an increased heart rate (10–15 bpm) and increased stroke volume, with relatively constant blood pressure. Motility, acidity and tone of GIT are decreased during pregnancy and this might interfere with drug absorption or excretion and finally drug metabolism may be affected at certain stages of pregnancy.[34] For example, changes in antidepressant metabolism and dosing during pregnancy and early postpartum were reported.[45] More so, in pregnant condition, due to large body water, hormonal environment, any drug taken by mother, fetus may get exposed to the same and lead to ADR especially if the drug is teratogenic.[46-47] The drug may affect fetus/neonate at different gestational stages either first trimester or second and third trimesters. Some drugs labeled as teratogenic such as anticonvulsants like phenytoin and valproates, alcohol, sedatives, opioids, LSD, cannabis, thalidomide and others comes with black box warning. [48] Pregnant mothers need to exercise utmost care while on any drug regimen with consultation of concerned physician.

Race: Ethnicity and race is an important factor responsible for inter individual variability in drug responses and exposure to various ADR. This is explained by polymorphism due to genetic variation encoding drug metabolizing enzymes, drug transporters, and receptors. [49] Many races are more prone to some ADR than others, being unable to metabolize some drugs because of lack of certain enzymes or mutation of pseudo variety of the same. For example, A deficiency of the enzyme glucose 6-phosphatedehydrogenase (6-GPD) may lead to hemolysis (also known as favism) in the patients taking some food such as fava beans or medications (antioxidant drugs like primaquine and dapsone) or because of illness due to bacterial or viral infection. It is particularly common in people of Mediterranean and African origin. [50] Isonizid causes peripheral neuropathy in slow acetylaters (due to higher drug concentration) and hepatotoxicity in fast acetylaters (due to excess drug metabolites). [51] African Americans were found to be more susceptible to developing ACE-related angioedema than other ethnic groups, in one study.[52] Caucasian race were reported to be more prone to the hypersensitivity reactions to abacavir. [53] Black patients were reported to have higher risk of angioedema and the risk of intracranial hemorrhage than non-black patients.[54]

A particular genotype 1A9 genotypes with UDP-glucuronosyltransferase in Parkinson's disease patients were found to be susceptible to catechol-*O*-methyltransferase inhibitors and were found to be prone to ADRs leading to treatment withdrawal.[55] There are many such examples due to polymorphism depending on the nature of the ADRs; sometime involving more than one gene.[56]

Concomitant diseases: some pre existent co-morbid conditions can also expose to various ADR. As liver contains the enzyme system *Cytochrome P-450* responsible for metabolism of many drugs, any diseases such as cirrhosis or hepatotoxicity may lead to decreased metabolism of that particular drug and thus increasing its concentration in body leading to ADR due to toxicity. Similarly in case of existing renal diseases or reduced renal function, as kidney is the major excretory organ of body. Conditions such as hypo albuminemia, shock or cardiovascular disease decrease the protein concentration in body increasing free concentration of drug in the body and leading to toxicity attributed to ADR. The episodes of cough could be exacerbated in patients with asthma taking beta blockers for hypertension. Beta blockers may cause serious medical problems if taken by diabetic patients because of risk of hypoglycemia. Patients suffering from peptic ulcer may have serious medical

consequences if some drugs like NSAIDS are prescribed. Vitamin B6 is recommended to be used to prevent isoniazid-induced B_6 deficiency and neuropathy in people with a risk factor, such as pregnancy, lactation, HIV infection, alcoholism, diabetes or kidney failure. [57] People with liver dysfunction are at a higher risk for hepatitis caused by INH, and may need a lower dose.[58] Any coexistent disease also necessitates the administration of many medicines together that increase the potential further for ADR due to probability of various drug-drug or herbal drug interactions, if proper precaution is not taken.

Multiple medications: Poly pharmacy, unless and until adopted for the beneficial effects in therapy as per the advice of the physician, is harmful and predispose the patients to ADR as the number of drugs taken together may interact among themselves modifying the overall effects. [59] Prescription medications, over the counter medicines or even herbal products, if taken together, may interact together; increasing or cancelling the effects of one another and exposing patient to various ADR. Multiple medication administration also largely depends upon the patient behaviour and compliance to the medical regimen prescribed.

Patient behavior: an effective patient compliance in therapy is a very important factor in success of any therapy. If patients indulge in certain behavior such as visiting multiple physicians, resorting to self medication, having harmful dietary habits like smoking, using tobacco, alcohol and other addictive substance of abuse along with prescribed therapy it would lead to exposure to various ADR. Or utter non-compliance in taking the dose of medicine because of forgetful behavior and doubling the dose of same to make up for the loss dose-the behaviour pattern which is so common in elderly could also predispose patients to various ADR.[60-61]

Classifications: ADR can be classified on basis of onset or incident such as late or early or on basis of severity as, mild, moderate to severe. As per the physicians perspectives, the ADR is also classified as, Serious & life threatening (Anaphylactic Shock, hemolysis), affecting quality of life (impotence, hirsutism) or minor with nuisance value (nausea, vomiting, constipation, diarrhea). One of the traditional classifications is based on the pharmacological mechanisms, such as proposed by 'Rawlins and Thompson'. [62] It described type 1 or A (Augmented reactions), type 2 or B (Bizarre reactions). But this classification was self limiting and does not include all other types of ADR. So another classification was put forward by 'Wills and Brown', which divide ADRs in to 09 categories as type A (Augmented), type B (Bugs)-microorganism related, type C (Chemical), Type D (Delivery),

type, E (Exit), type F (Familial), type G (Genotoxicity), type H (hypersensitivity) and type U (Unclassified).[63] (Table 1: Wills and brown classification of adverse drug reactions (ADRs). Over the years, many new classification systems for adverse drug reactions were suggested based on time course and susceptibility as well as dose responsiveness. A three dimensional classification system based on dose relatedness, timing, and patient susceptibility (DoTS), to improve drug development and management of ADRs was reported. [64] The main five types of ADR are as given below.[65]

Type A (Augmented) reactions: Type 1 or A reactions results from the exaggeration of normal pharmacological actions of the drugs when given in normal therapeutic doses. The patients may experience type A ADR when the drug's action is augmented. Drugs acts on the receptor which is a specific molecule in the body such as protein and produces the pharmacological effects. For instance, drug levodopa acts on dopamine receptor (D_1). Higher the dose of the drug leads to greater the actions on the receptor which thus leads to the greater effects. It is a therapeutically desired effect that levodopa- carbidopa combination relieves the symptoms of parkinsonism but unfortunately the bad effects are nausea and vomiting, tachycardia, hypotension and psychotic problems such as schizophrenia. This type of ADR can be produced by various mechanisms. The main characteristics of these reactions are:

- These are the most common type of ADR (nearly 80% of all ADR)
- These occur at normal doses, are dose dependent and get more severe with higher doses.
- They tend to resolve on dose reduction.
- These are pharmacologically predictable as mechanism is known.
- These unusually cause low mortality and not usually serious.
- They are pharmacologically reproducible being able to be studied experimentally.

The main mechanisms behind type A reactions are as follows.

a. A primary therapeutic action of drug at its primary site. e.g. lowering of blood pressure by anti hypertensive drugs, bradycardia by beta blockers.[66] and hemorrhage with anticoagulants.[67]
b. A primary action at site different from the therapeutic sites. e.g. gastrointestinal bleed with the use of NSAIDS like aspirin, a pain relieving medication which also inhibit platelet aggregation.[68]

c. Secondary actions of the drug. Dry mouth with tricyclic antidepressant like imipramine, which is basically monoamine re-uptake inhibitors, can also inhibit cholinergic receptors.[69]

Prevention: Type A reactions could be avoided by taking in to consideration the predisposing factors beforehand like pharmacogenetics (glucose 6-GPDdeficinecy can cause hemolysis in patients taking antioxidant drugs like primaquine o dapsone), adjusting the dose of drugs according to renal or hepatic functions (dose of aminoglycoside has to be reduced in patient with renal failure) and starting therapy with low dose titration and gradually increasing the dose to the therapeutic dosage (antihypertensive and blood pressure, anti depressants therapy) . In these types of ADR, it may be necessary to alter the route of administration or substitute the offending drug with another. In most cases, drugs with the same mechanism of action should be avoided.

Type B (Bizarre) reactions

Type 2 or B reactions are idiosyncratic reactions, may occur only rarely and only in some individuals, depending on the characteristics of the patients. These reactions do not occur in every patient with the same drugs. Following are the main characteristics.

- They are less frequent than type A, occurs only rarely.
- The effects are not related to the dose of the drugs.
- These reactions do not respond to the dose adjustments and generally the drug needs to withdrawn once these effects are produced.
- The reactions are not pharmacologically predictable as mechanism is not known.
- They are usually serious and may at times be even life threatening.
- They are not at all pharmacologically reproducible and can not be studied experimentally.

Type B reactions are further of two main types. 1. Immunological or allergic and 2. Non immunological or idiosyncratic.

1. **Immunological or allergic reactions:** The immunological reactions are those which involve allergic anybodies and occur with the prior exposure of the antigen. These are hypersensitivity reactions which happen due to exaggerated immunological response to drug or excipients, as a qualitative response rather not related to the amount of the drug. Many times body reacts immunologically to a variety of drugs but hypersensitivity refers only to reactions which are undesired and harmful. The common four types are as follows, as per Gell and Coombs system of classification.[70]

a. Type I. Anaphylactic or immediate hypersensitivity reactions.
b. Type II. Cytotolytic or cytotoxic reactions.
c. Type III. Arthus reactions
d. Type IV. Delayed hypersensitivity reactions.

Type I. Anaphylactic reactions happens when patient is sensitized due to first exposure of drug and IgE type of antibodies are generated in body which get fixed to the mast cells. On second exposure to the drug, antigen-antibody reaction follows, causing release of secondary mediators like prostaglandins (PGs), leukotrienes, platelet activating factor (PAF) and histamines, leading to vasodilation, bronchoconstriction, itching and edema. The well known example is penicillin induced allergy and anaphylactic shock.[71]

Type II Cytotoxic reactions takes place when the drug in question, gets combined with some cell components like proteins in body and sensitizing the patient on first exposure. IgG and IgM types of antibodies are generated against this antigen (drug-protein complex) and get attached to different cells like RBC. On second exposure, antigen-antibody reaction causes the destruction of the cell to which antibodies are attached, making the call to be an innocent bystander. The consequences may range from hemolysis, agranulocytosis, thrombocytopenia to aplastic anemia.[72] Penicillin induced anemia is one such example.[73]

Type III Arthus reactions [74] results from generation of IgG types of antibodies following sensitization of patients after first exposure. These antibodies float freely in the blood. On second exposure, to the drug, due to antigen-antibody reaction, there are formations of complexes which get lodged in to periphery, attaching to capillaries and produce endothelial damage. This leads to the release of lysosomes followed by vascular inflammatory response rash, serum sickness, fever, arthralgia and lymphadenopathy. Drugs like phenylbutazone and sulfonamide can produce this reaction in susceptible individuals.

Type IV delayed hypersensitivity reactions are cell mediated reactions.[75] unlike I-III which are antibody mediated reactions. In these reactions, when the patient is sensitized on first exposure to a drug, new T lymphocytes with receptors are generated for that drug. On second exposure, that drug as antigen gets attached to sensitized T lymphocytes. Lymphokines are released and granulocytes are attached as a result and leading to contact dermatitis or granuloma formation. Examples of drugs causing these types of reactions are topical antibiotics and local anesthetics.

Prevention: the management of anaphylactic reaction is crucial and life saving it largely depends on the type and gravity of the reaction. The offending drug in question is to be immediately discontinued. The traditional symptomatic measures are applied as in case of Anaphylactic shock, keeping the airway intact, fluid level correction and injecting the drugs like adrenaline (0.5 ml of 1: 1000 im or 3-5ml of 1: 10,000 IV as a drug of choice in anaphylaxis), or other sympathomimestics like noradrenaline or dopamine, other bronchodilator, steroid (100 mg iv or 1-4 mg/kg/day for 5 to 7days) and antihistaminics depending on the type of allergic reaction and situation. Plasmapharesis (removal of blood and replacement plasma with fresh frozen plasma or albumin may be used anecdotally as an adjunctive therapy. The doctors must get the history of hypersensitivity of the drug to be prescribed. The known hypersensitivity or the drug is an absolute contraindication for that drug. Sensitization tests are also conducted in patient prior to administration in patients susceptible to that drug. Taking medical record and history of patient becomes an essential tool. If hypersensitivity is present without the history of prior administration, it does not rule out the diagnosis of hypersensitivity as the patient may get sensitized through breast milk or dairy products (if the drug is administered to animals).

2. **Non Immunological or idiosyncratic reactions**

These reactions as the name suggests are totally bizarre and unpredictable do not involve allergic antibodies and can occur without prior exposure. [76] Symptoms may range from rash, hives breathing difficulties, swelling of body parts or the symptoms due to inflammations or damaged functions of body vital part, depending on the reactions caused. Few examples of drugs causing such kinds of reactions are antibiotics like penicillins, tetracyclines, sulfonamides and cephalosporins, phenothiazines, barbiturates and anesthetics like haloperidol. Few examples are as follows with brief explanations.

- **Prolong duration of apnea in some patients by succinylcholine due to atypical pseudo cholinesterase:.**[77] Succinylcholine is a neuromuscular blocker drug employed during surgery to induce a brief paralysis. The enzyme cholinesterase is required for metabolism of this drug, so that brief action of the drug is over in 1-6 minutes and patient revives after the same after completion of surgical procedure. If the patient is lacking this particular enzyme or having atypical, pseudo cholinesterase enzyme, the drug is not metabolized and its action lasts for much longer than required exceeding its normal duration of action. The consequences will be a prolong apnea in patient as the diaphragm

remains paralyzed and patient would not be able to breathe on its own. If any artificial mean of ventilation is not employed and the situation is not counteracted properly, patient may go into coma and death may result.

- **Hemolysis in patients with 6-GPD deficiency by primaquine, dapsone and other oxidizing drugs:** [78-79] *Glucose-6-dehydrogenase* is required for the stability of RBC. G-6PD converts *glucose-6-phosphate* into *6-phosphoglucono-δ-lactone* and is the rate-limiting enzyme of this metabolic pathway that supplies reducing energy to cells by maintaining the level of the reduced form of the co-enzyme *nicotinamide adenine dinucleotide phosphate* (NADPH). The NADPH in turn maintains the supply of reduced glutathione in the cells that is used to mop up free radicals that cause oxidative damage. The G6PD / NADPH pathway is the only source of reduced glutathione in red blood cells (erythrocytes). When the patient takes antioxidant drugs like primaquine, it reduced the glutathione due to oxidative stress leading to loss of stability of RBC resulting in hemolysis.

- Porphyria caused by barbiturates: Acute intermittent porphyria (AIP) is a rare autosomal dominant metabolic disorder affecting the production of heme, the oxygen-binding prosthetic group of hemoglobin. [80-81] It is characterized by a deficiency of the enzyme *porphobilinogen deaminase*. Under normal circumstances, heme synthesis begins in the mitochondrion, proceeds into the cytoplasm, and finishes back in the mitochondrion. However, without *porphobilinogen deaminase*, a necessary cytoplasmic enzyme, heme synthesis cannot finish, and the metabolite porphobilinogen accumulates in the cytoplasm leading to AIP. Symptoms in AIP can be variable. They include, Abdominal pain which is severe and poorly localized (most common, 95% of patients experience), Urinary symptoms (Dysuria, urinary retention/incontinence or dark urine), Peripheral neuropathy (patchy numbness and paresthesias), Proximal motor weakness (usually starting in upper extremities which can progress to include respiratory impairment and death), Autonomic nervous system involvement (circulating catecholamine levels are increased, may see tachycardia, hypertension, sweating, restlessness and tremor), Neuropsychiatric symptoms (anxiety, agitation, hallucination, hysteria, delirium, depression), Electrolyte abnormalities (Hyponatremia may be due to hypothalamic involvement leading to SIADH that may lead to seizures). Unlike other porphyrias, rash is not typically seen in AIP.

Hematin and heme arginate are the drugs of choice in acute porphyria, in the United States and the United Kingdom, respectively. These drugs need to be given very early in an attack to be effective. Effectiveness varies among individuals. They are not curative drugs, but can shorten attacks and reduce the intensity of an attack. Side-effects are rare but can be serious. These heme-like substances, in theory, inhibit ALA synthase and, hence, the accumulation of toxic precursors. A high-carbohydrate (10% glucose) infusion is recommended, which may aid in recovery. If drugs have caused the attack, discontinuing the offending substances is essential. Infection is one of the top causes of attacks and requires vigorous treatment. The treatments are symptomatic for the resultant infection, pain or seizure.

- **Malignant hyperthermia by halothane:** It is a rare life-threatening condition that is usually triggered by exposure to certain drugs used for general anesthesia, specifically the volatile anesthetic agents and the neuromuscular blocking agent succinylcholine. [82] In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated quickly.[83] This condition is known by a number of names, including malignant hyperthermia (MH), malignant hyperthermia syndrome (MHS), malignant hyperthermia susceptibility (MHS), and malignant hyperpyrexia. The typical symptoms of malignant hyperthermia are due to a hypercatabolic state, which presents as a very high temperature, an increased heart rate and breathing rate, increased carbon dioxide production, increased oxygen consumption, acidosis, rigid muscles, and rhabdomyolysis. The symptoms can develop any time during the administration of the anesthetic triggering agents. It is difficult to find confirmed cases in the postoperative period more than several minutes after discontinuation of anesthetic agents. There is no simple, straightforward test to diagnose the condition. When MH develops during a procedure, treatment with dantrolene sodium is usually initiated; dantrolene and the avoidance of inhaled anesthesia in susceptible people have markedly reduced the mortality from this condition.[84] Dantrolene is a muscle relaxant that appears to work directly on the ryanodine receptor to prevent the release of calcium. After the widespread introduction of treatment with dantrolene, the mortality of malignant hyperthermia fell from 80% in the 1960s to less than 5%. Dantrolene remains the only drug known to be effective in the treatment of

MH. It is recommended that each hospital keeps a minimum stock of 36 dantrolene vials (720 mg) sufficient for a 70-kg person.

Prevention: prevention of these idiosyncratic reactions are totally symptomatic most of the time and the drug responsible causing such reaction needs to be stopped immediately.

Type C (Continuous, chronic, cumulative use of drugs) reactions:

Type 3 or C chemical reactions are those reactions whose biological characteristics are attributed to either the chemical structure of the parent drug or of the reactive intermediates and metabolites. These reactions, as the name suggests may happen because of long term, chronic use of the drug, which lead to introduction of the new spontaneous disease in the patient or cause change in the frequency of natural disease that may occur in the lifetime of an individual. This may manifest as a result of increase rate of spontaneous disease, as a result of adaptive changes or tolerance. The characteristics of these types of reactions are as follows.

- Often have a long latency
- Not specific for the drug
- The mechanisms are not clearly known
- The effect is not reproducible.

Some well known examples of these reactions are mentioned below.

Hepatotoxicity caused by the high doses of Paracetamol: Paracetamol (also called acetaminophen in North America) toxicity is caused by excessive use or overdose of the analgesic drug paracetamol. [85] Mainly causing liver injury, paracetamol toxicity is one of the most common causes of poisoning worldwide. The drug has an excellent safety profile otherwise, when administered in proper therapeutic doses. Many individuals with paracetamol toxicity may have no symptoms at all in the first 24 hours following overdose. Others may initially have nonspecific complaints such as vague abdominal pain and nausea. With progressive disease, signs of liver failure may develop; these include low blood sugar, low blood pH, easy bleeding, and hepatic encephalopathy. Some will spontaneously resolve, although untreated cases may result in death. Damage to the liver, or hepatotoxicity, results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI) (also known as N-acetylimidoquinone). NAPQI depletes the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure. Risk factors for toxicity include excessive chronic alcohol intake, fasting or anorexia

nervosa, and the use of certain drugs such as isoniazid. Treatment is aimed at removing the paracetamol from the body and replacing glutathione. Activated charcoal can be used to decrease absorption of paracetamol if the patient presents for treatment soon after the overdose; the antidote N- acetylcysteine (NAC) acts as a precursor for glutathione, helping the body regenerate enough to prevent damage to the liver. N-acetylcysteine can neutralize NAPQI by itself as well. [86-87] A liver transplant is often required if damage to the liver becomes severe. Patients treated early have a good prognosis, whereas patients that develop major liver abnormalities typically have a poor outcome. Efforts to prevent paracetamol overdose include limiting individual sales of the drug and combining paracetamol with methionine, which is converted into glutathione in the liver.

Tardive dyskinesia caused by antipsychotics: This neurological disorder most commonly occurs in patients as the result of long-term or high-dose use of antipsychotic drugs or as a side effect from usage of drugs for gastrointestinal disorders in children and infants. [88] It is a difficult-to-treat and often incurable form of dyskinesia, a disorder characterized by repetitive, involuntary, purposeless movements. Some examples of these types of involuntary movements include grimacing, tongue movements, lip smacking, lip puckering and excessive eye blinking. The exact mechanism of the disorder remains largely uncertain. The most compelling line of evidence suggests that tardive dyskinesia may result primarily from neuroleptic-induced dopamine supersensitivity in the nigrostriatal pathway, with the D_2 dopamine receptor being most affected.[89] Neuroleptics act primarily on this dopamine system, and older neuroleptics, which have greater affinity for the D_2 binding site, are associated with high risk for tardive dyskinesia. Primary prevention of tardive dyskinesia is achieved by using the lowest effective dose of a neuroleptic for the shortest time. However, with diseases of chronic psychosis such as schizophrenia, this strategy must be balanced with the fact that increased dosages of neuroleptics are more beneficial in preventing recurrence of psychosis. If tardive dyskinesia is diagnosed, the causative drug should be discontinued. Tardive dyskinesia may persist after withdrawal of the drug for months, years or even permanently. Some studies suggested that physicians should consider using atypical antipsychotics as a substitute to typical antipsychotics for patients requiring medication. These agents are associated with fewer neuromotor side effects and a lower risk of developing tardive dyskinesia.[90] Recent studies have tested the use of melatonin, high dosage vitamins, and different antioxidants along with antipsychotic drugs as a way of preventing and treating tardive dyskinesia.[91-91] Some other drugs have shown efficacy like

tetrabenazine, which is a dopamine depleting drug, is sometimes used to treat tardive dyskinesia and other movement disorders. However, it is only approved to treat chorea associated with Huntington's disease. Reserpine, α-methyldopa, Ondansetron (Zofran), and a variety of anti-Parkinsonian medications such as donepezil, baclofen, and pramipexole have also been tried in various studies as a treatment for TD with some success.[92-95] Some other potentially beneficial drugs reported for TD are Clonidine, botox injections (for minor focal dystonia only), clonazepam, vitamin B6 and the branched-chain amino acid formula Tarvil, containing the amino acids valine, isoleucine, and leucine in a 3:3:4 ratio in males, but their use is limited by related side effects.[96]

Analgesic nephropathy caused by phenacetin: it is an injury or damage to the kidney caused by excessive use of the analgesic medications such as phenacetin, or aspirin or even paracetamol.[97-98] The specific kidney injuries induced by analgesics are renal papillary necrosis and chronic interstitial nephritis. They appear to result from decreased blood flow to the kidney, rapid consumption of antioxidants, and subsequent oxidative damage to the kidney. This kidney damage may lead to progressive chronic kidney failure, abnormal urinalysis results, high blood pressure, and anemia. A small proportion of individuals with analgesic nephropathy may develop end-stage kidney disease. The mechanism of action is unclear as to how phenacetin induces injury to the kidney. But it was proposed that phenacetin's metabolites lead to lipid peroxidation that damages cells of the kidney. [99] Paracetamol is the major metabolite of phenacetin which may contribute to kidney injury through a specific mechanism. In cells of the kidney, cyclooxygenases catalyse the conversion of paracetamol into N-acetyl-p-benzoquinoneimine (NAPQI). This NAPQI depletes glutathione via non-enzymatic conjugation to glutathione, a naturally occurring antioxidant. And with the depletion of glutathione, cells of the kidney become particularly sensitive to oxidative damage. Treatment of analgesic nephropathy begins with the discontinuation of analgesics, which often halts the progression of the disease and may even result in normalization of kidney function.[100]

Other examples of such continuous, chronic ADR are thromboembolic complications and possible influence on breast tumor by long term, systemic use of oral contraceptives.[101-102]

Type D (Delayed) reactions

Type 4 or D reactions occur on prolong use of drugs after many years after the treatments. Dysmorphogenic side effects and teratogenic side effects are the two main types of adverse

effects included in these types of reactions. While dysmorphogenesis is an abnormal tissue formation, teratogenesis is the abnormalities of physiological development.[103] It is often thought of as the study of human congenital abnormalities, but it is broader than that, taking in other non-birth developmental stages, including puberty. Some known teratogens include, thalidomide, phenytoin, carbamazepine, valproic acid, warfarin. lithium and methotrexate. Some examples of Type D reactions are as follows.

Skeletal malformation with thalidomide:.[104] Thalidomide was released in to market in 1958 in West Germany under the label of "Contergan". Primarily prescribed as a sedative or hypnotic, thalidomide also claimed to cure "anxiety, insomnia, gastritis, and tension". Afterwards it was used against nausea and to alleviate morning sickness in pregnant women. Thalidomide became an over-the-counter drug in Germany around 1960, and could be bought without a prescription. Shortly after the drug was sold, in Germany, between 5,000 and 7,000 infants were born with phocomelia, an extremely rare congenital disorder involving loss or malformation of the limbs (dysmelia). Patients that receive a loss of limbs due to phocomelia are typically treated with prosthetics, which is a synthetic alternative for missing limbs, teeth, and various other body parts.

Fetal hydantoin syndrome with Phenytoin:.[105] also called 'fetal dilantin syndrome' is a group of defects caused to the developing fetus by exposure to the teratogenic effects of phenytoin or carbamazepine. Dilantin is the brand name of the drug phenytoin sodium in the United States, commonly used in the treatment of epilepsy. It may also be called congenital hydantoin syndrome. About one third of children whose mothers are taking this drug during pregnancy typically have intrauterine growth restriction with a small head and develop minor dysmorphic craniofacial features and limb defects including hypoplastic nails and distal phalanges (birth defects). A smaller population may have growth problems and developmental delay, or mental retardation. Methemoglobinemia is a rarely seen side effect. Heart defects and cleft lip may also be featured.

Contradi syndrome with use of warfarin:[106] also known as 'contradi-Hünermann–Happle' syndrome) is a form of an autosomal-dominant form of chondrodysplasia punctata, a group of rare genetic disorders of skeletal development involving abnormal accumulations of calcium salts within the growing ends of long bones. It is commonly associated with mild to moderate growth deficiency, disproportionate shortening of long bones, particularly those of the upper arms and the thigh bones, short stature, and/or curvature of the spine. In rare cases,

intellectual disability may also be present. While evidence suggests that this particular syndrome predominantly occurs in females and is usually inherited as an X-linked dominant trait, rare cases in which males were affected have also been reported. The syndrome is also associated with maternal use of warfarin sodium during pregnancy.

Treatment can involve operations to lengthen the leg bones, which involves many visits to the hospital. Other symptoms can be treated with medicine or surgery. Most female patients with the syndrome can live a long and normal life, while males have only survived in rare cases.

Neural tube defects (NTDs) with carbamazepine.[107] Carbamazepine has been assigned to pregnancy category D by the FDA. Some antiepileptic drugs including carbamazepine can cause fetal harm when administered to a pregnant woman. Epidemiological data suggested that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including *spina bifida*, collectively called neural tube defects, a group of conditions in which an opening in the spinal cord or brain remains from early in human development in the 3rd week of pregnancy. [108] Treatments of NTDs depend on the severity of the complication. No treatment is available for anencephaly and infants usually do not survive more than a few hours. Aggressive surgical management has improved survival and the functions of infants with *spina bifida*. Food and Drug Administration published regulations requiring the addition of folic acid to enriched breads, cereals, flour and other grain products foods fortified with folic acid or take supplements in addition to eating folate-rich foods to reduce the risks of serious birth defects.[109]

Cleft lip, cleft palate and cardiac defects with the use of corticosteroids: [110] Evidence for the teratogenicity of corticosteroids in humans is limited and has resulted in inconsistent recommendations regarding their use during early pregnancy. The two main types of oral clefts are cleft lip and cleft palate. Cleft lip is the congenital failure of the maxillary and median nasal processes to fuse, forming a groove or fissure in the lip. Cleft palate is the congenital failure of the palate to fuse properly, forming a grooved depression or fissure in the roof of the mouth. Clefts of the lip and palate can occur individually, together, or in conjunction with other defects. Physicians may be wary of prescribing corticosteroids because preclinical studies in rodents and rabbits have demonstrated that high doses consistently cause cleft palate.[111]

Type E (End of the use) reactions: these are end of the use reactions related to discontinuation of the treatment that is too abrupt. These occur after the drug has been stopped abruptly. Drug withdrawal reactions are included in this category. Examples are: adrenocortical insufficiency or addisonian crisis following withdrawal of corticosteroids. It is a condition in which the adrenal glands do not produce adequate amounts of steroid hormones, primarily cortisol; but may also include impaired production of aldosterone (a mineralocorticoid), which regulates sodium conservation, potassium secretion, and water retention. If not treated, adrenal insufficiency may result in severe abdominal pains, vomiting, profound muscle weakness and fatigue, depression, extremely low blood pressure (hypotension), weight loss, kidney failure, changes in mood and personality, and shock (adrenal crisis). [112] One of the major causes of acute adrenal insufficiency is the sudden withdrawal of long-term corticosteroid therapy. Also, it often occurs if the body is subjected to stress, such as an accident, injury, surgery, or severe infection; death may quickly follow. The treatment advised is, intravenous fluids, rest and intravenous steroid (Solu-Cortef/injectable hydrocortisone) later hydrocortisone, prednisone or methyl predisolone tablets.[113]

Rebound hypertension following sudden discontinuation of clonidine:[114] Clonidine is a sympatholytic medication used to treat high blood pressure, attention deficit hyperactivity disorder, anxiety disorders, withdrawal from either alcohol, opioids, or smoking, migraine, menopausal flushing, diarrhea, and certain pain conditions. It is classified as a centrally acting α_2 adrenergic agonist and imidazoline receptor agonist that has been in clinical use for over 40 years. Abrupt withdrawal of adrenergic blockers lie clonidine in a hypertensive subject may result in acute hypertensive crisis. This crisis results from marked increase in adrenergic discharge and upregulation of adrenoceptors. α- and β-blocking activities of labetalol may be particularly beneficial in a hyperadrenergic state following abrupt withdrawal of adrenergic blockers. Sudden withdrawal of drugs like benzodiazepines, tricyclic antidepressants or beta blockers can precipitate such reactions. These types of reactions may also be seen as the appearance of a symptom that did not exist before initiation of the therapy. For example, rebound convulsion may happen on withdrawal of carbamazepine in non-epileptic patients.[115] The wills and brown classification of ADR is mentioned below in table- I.

Table I. Wills and brown classification of adverse drug reactions (ADRs).[63]

Sr.No	Classification: Types of ADR	Characteristics	Examples
1.	Type A (Augmented),	Very Common, dose related, predictable Pharmacologically, can be counteracted by withdrawal of drugs, low mortality.	Bradycardia with Beta-blockers.
2.	Type B (Bugs)	Microorganism related, predictable, can be counteracted by withdrawal of drugs responsible.	Resistance due antibiotics overuse.
3.	Type C (Chemical),	Chemical and concentration related, irritant reactions.	Extravasations and phlebitis.
4.	Type D (Delivery)	Drug delivery related including nature of formulation, method of administration.	Infection at the site of injection or implant.
5.	Type, E (Exit),	Withdrawal reactions, Begins when drug is stopped or dose reduced.	Withdrawal reactions due to opioids, benzodiazepines, beta-blockers etc.
6.	Type F (Familial)	Occurs in Genetically predisposed individuals by lack or mutations of certain genes.	Hemolysis in patients with 6-GPD deficiency by primaquine, dapsone otheroxidizing drugs.
7.	Type G (Genotoxicity)	Developmental toxicity, irreversible genetic damage by teratogens.	Thalidomide induced fetus abnormalities.
8.	Type H (hypersensitivity)	Involving activation of immune system, antigen-antibody reactions.	Anaphylactic reactions by penicillin.
9.	Type U (Unclassified)	Unclassified due to unknown causes.	Drug related taste or smell disturbances caused by drugs like simvastatin, captopril

Pharmacovigilance in India: need of the hour: detection, assessment and reporting of hitherto unknown ADRs have become an urgent need of the hour today. Though the reporting of individual case safety reports (ICSRs) related to ADR due to allopathic as well as herbal drugs have increased in the recent years compared to past, the task still remains very challenging for India.[116] After the thalidomide tragedy WHO established international monitoring center at Uppsala to ensure patient safety in the year 1961. The Pharmacovigilance program of India (PvPI) started by the ministry of health and family welfare, Govt. of India with the vision of patient safety and welfare in Indian population, in the year 2010 with AIIMS, New Delhi as the national coordination center (NCC), which

shifted to Indian Pharmacopoeia commission (IPC) Ghaziabad, India in April, 2011. Total of 22 ADR monitoring centers were set across the country in the year 2010, which has increased to 90 by the end of 2012, according to PvpI report.[117] ADR Monitoring Centers (AMCs) under PvPI are set up all across India to collect the adverse event information. These AMCs are the Medical Council of India (MCI) approved medical colleges & hospitals, medical/central/autonomous institutes, public health programs or corporate hospitals. They are responsible for collecting the adverse event information from the patients, following up with them to check the completeness of the ADR reports as per Standard Operating Procedures (SOPs), entering information in the prescribed software (Vigiflow) and sending them to NCC via the same software. Each AMC at 24 local peripheral centers send spontaneous case reports to the 06 regional centers which send them to 02 Zonal centers, which submit the same to NCC. All these reports are then sent to the WHO ADR Monitoring Centre at Uppsala. Furthermore, the Health Ministry of India approved in March 2015, the 'Materio Vigilance Programme of India' (MvPI) to monitor Medical Device associated Adverse Events (MDAE) and coordinated by the Indian Pharmacopoeia Commission (IPC) in collaboration with the Central Drug Standard Control Organization (CDSCO). [118] Recent important initiatives undertaken by PvPI include the provision of a toll-free number (1800 180 3024), as well as mobile app, apart from mail and website links and also the introduction of AE reporting forms in six regional languages to encourage consumer reporting. The ADR reporting forms for health professionals and for consumers are available on CDSCO website.[119] The methods of estimation.[120] and pharmaco-epidemiological methods of detection ADR are reported for better pharmacovigilance, including spontaneous reporting system,[121] yellow card system in UK,[122] prescription event monitoring, and public health data surveillance, which are all hypothesis generating methods. While cohort, case control studies and randomized controlled trials are the hypothesis testing methods.[123] Pharmacovigilance methods for reporting and detection in detail are the matter of another long discussion and review paper.

Current Scenario: Underreporting of the ADR is the perennially chronic problem, not only in India but worldwide. Though, India is making progressive strides in the direction of effective pharmacovigilance and reporting of individual case safety reports (ICSR) are on rise but still we need to take more proactive steps to improve the scenario further to ensure the safety of the population.[124-125] This is especially when we have the diverse systems of alternative therapies prevalent among the masses in the country. The pharmacovigilance of

herbal medicines poses the unique challenge and the safety concerns in this area become even more important.[126] The role of all, health practioners as prescribers including Ayurvedic doctors, pharmacists, patients and pharmaceutical manufacturers and even consumers calls for lot more interventions.[127] If reporting of ADR is increased with lot more awareness among public and newer approach to modify existing methods along with greater consideration of pharmacogenetics and pharmacogenomics, it will optimize the safety of medicines including herbal counterparts.

REFERENCES

1. Miller MT. "Thalidomide Embryopathy: A Model for the Study of Congenital Incomitant Horizontal Strabismus". Transaction of the Am Ophthalmol Soc 1991; 81: 623–674.
2. herapontos C, Erskine L, Gardner ER, Figg WD, Vargesson N (May 2009). "Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation". Proc Natl Acad Sci 2009; 106(21): 8578.
3. Vargesson N. "Thalidomide-induced teratogenesis: history and mechanisms". Birth Defects Res C Embryo Today. 2015; 105(2): 140–56.
4. Greene, W. The emergence of India's pharmaceutical industry and implications for the US generic drugs market, Working paper no. 2007-05-A, Office of Economics, US International Trade Commission, Washington, DC. 2007.
5. Indian Pharmaceutical Industry IBEF, Ministry of Commerce and Industry, Government of India (2013) http://www.ibef.org/industry/pharmaceutical-india.aspx [accessed: January 27, 2017].
6. Akhtar G. Indian Pharmaceutical industry: an overview. IOSR Journal Of Humanities And Social Science (IOSR-JHSS) 2013; 13(3): 51-66 e-ISSN: 2279-0837, p-ISSN: 2279-0845. www.Iosrjournals.Org www.iosrjournals.org 51 | Page Indian]. (Accessed: November 23, 2016).
7. Anonymous. Indian Pharmaceutical industry. India brand equity foundation (IBEF). Updated on September, 2016. http://www.ibef.org/industry/pharmaceutical-india.aspx] [Accessed: November 23, 2016].
8. Edwards IR, Aronson JK. Adverse drug reactions: Definition, diagnosis and management. Lancet 2000; 356:1255–9.
9. Davies DM. History and epidemiology. In: In: Davies DM, editor. Textbook of adverse drug reactions. Vol. 1. Oxford: Oxford University Press; 1977. p. 7.

10. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977; p. 10.
11. Jemal A. Ward E. Hao Y. Thun M. Trends in the leading causes of death in the United States in years 1970–2002. JAMA. 2005; 294: 1255–1259.
12. World Health Organization (WHO). (2011) [Online]. http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf [accessed: January 27, 2017].
13. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997; 277: 301.
14. McIntyre J, Choonara I. "Drug toxicity in the neonate." Biol Neonate 2004; 86(4): 218–21.
15. Kurian J, Mathew J, Sowjanya, K et al. Adverse Drug Reactions in Hospitalized Pediatric Patients: A Prospective Observational Study. Ind J Pediatr 2016; 83: 414.
16. Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 2008; 94: 724–728.
17. De-gregori S, Ranzani GN, Borghesi A, et al. Drug transporters and renal drug disposition in the newborn. J. Matern Fetal Neonatal Med 2009; 22: 31–37.
18. Anderson GD, Lynn AM. Optimizing pediatric dosing: a developmental pharmacologic approach. Pharmacother 2009; 29(6): 680–690.
19. Ibáñez L, López-Bermejo A, Díaz M, et al. Abdominal fat partitioning and high-molecular-weight adiponectin in short children born small for gestational age. J Clin Endocrinol Metab 2009; 94(3): 1049–1052.
20. Schoderboeck L, Adzemovic M, Nicolussi EM, et al. The window of susceptibility for inflammation in the immature central nervous system is characterized by a leaky blood–brain barrier and the local expression of inflammatory chemokines. Neurobiol Dis 2009; 35(3): 368–375.
21. Pellicer A, Bravo MC, Madero R, et al. Early systemic hypotension and vasopressor support in low birth weight infants: impact on neurodevelopment. Pediatr 2009; 123(5): 1369–1376.
22. Kaur S, Kapoor V, Mahajan R, et al. Monitoring of incidence, severity, and causality of adverse drug reactions in hospitalized patients with cardiovascular disease. Ind J Pharmacol. 2011; 43(1): 22–26.

23. Vennila V, Madhu V, Rajesh R, et al. Tetracycline-Induced Discoloration of Deciduous Teeth: Case Series. J Int Oral Health 2014; 6(3): 115–119.
24. Mulhall A, de Louvois J, Hurley R. "Chloramphenicol toxicity in neonates: its incidence and prevention". Brit Med J (Clin Res ed.) 1983; 287(6403): 1424–7.
25. Higuera V. The Dangers of Gray Baby Syndrome in Infants. [Available from http://www.healthline.com/health/parenting/gray-baby-syndrome#1 April 29, 2016]. [Accessed: November 29, 2016].
26. Orlowski JP, Hanhan UA, Fiallos MR. "Is aspirin a cause of Reye's syndrome? A case against". Drug Saf 2002; 25(4): 225–31.
27. Schrör, K. "Aspirin and Reye syndrome: a review of the evidence."Paediatr drugs 2007; 9(3): 195–204.
28. Bates DW, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001; 285(16):1107–1116.
29. Alhawassi TM, Krass I, Bajorek BV, et al. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging 2014; 1;9: 2079-86.
30. Brahma DK, Wahlang JB, marak MD et al. Adverse drug reactions in the elderly. J Pharmacol Pharmacother 2013; 4(2): 91–94.
31. Budnitz DS, Shehab N, Kegler SR, et al. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med 2007; 147:755–765.
32. Jimmy J, Padma GMR. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 2006; 54: 226–233.
33. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009; 41(2):67–76.
34. Alomar, MJ. Factors affecting the development of adverse drug reactions (Review article). Saudi Pharm J 2014; 22(2): 83–94.
35. Hughes SG. Prescribing for the elderly patients: Why do we need to exercise caution? Br J Clin Pharmacol. 1998; 46: 531–3.
36. Waxman DJ, Holloway MG. Sex differences in the expression of hepatic drug metabolizing enzymes. Mol Pharmacol 2009; 76: 215–228.

37. Labbé L, Sirois C, Pilote S. Effect of gender, sex hormones, time variables and physiological urinary pH on apparent CYP2D6 activity as assessed by metabolic ratios of marker substrates. Pharmacogenetics. 2000; 10: 425–438.
38. El-Eraky H, Thomas SHL. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. Br J Clin Pharmacol 2003; 56: 198–204.
39. Ofotokun I., Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. Top. HIV Med. 2003; 11(2): 55–59.
40. Bing Z, Liu ZQ, Chen GL, et al. The distribution and gender difference of CYP3A activity in Chinese subjects. J Clin Pharmacol 2003; 55: 264–269.
41. Rajani S., Subba RB, Bhawana S. Incidence of Hepatotoxicity Due to Antitubercular Medicines and Assessment of Risk Factors. Ann Pharmacother 2004; 38(6): 1074–1079.
42. Rodenburg EM, Stricker BH, Visser LE. Sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions. Br J Clin Pharmacol. 2012; 74(6): 1045–1052.
43. Singh NP, Uppal M, Anuradha S, et al. Angiotensin converting enzyme inhibitors and cough-a north Indian study. J. Assoc. Physicians India. 1998; 46(5): 448–451.
44. Mitchell SC, Smith R, Waring RH. The menstrual cycle and drug metabolism. Curr Drug Metab 2009; 10(5): 499–507.
45. Dorothy KS, Perel JM., Helsel JC, et al. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. Psychiatry. 2008; 69(4): 652–658.
46. Fraumeni JF, Chemicals in Human Teratogenesis and Transplacental Carcinogenesis. Pediatr 1974; 53(5): 807.
47. Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci Spring 2010; 40(2): 99-114.
48. Hill DS, Wlodarczyk BJ, Palacios Teratogenic effects of antiepileptic drugs. Expert Rev Neurother. 2010 Jun; 10(6): 943–959.
49. David E.O., Lee K.J., Philips A.K., Sadee W., Veenstra L. Potential role of pharmacogenomics in reducing adverse drug reactions. JAMA. 2001; 286(18): 2270–2279.
50. Frank JE. "Diagnosis and management of G6PD deficiency". Am Fam Phy 2005; 72(7): 1277–82.
51. Pande JN, Pande A, Singh SPN. Acetylator status, drug metabolism and disease. Natl Med J Ind 2003; 16: 24–6.

52. Morimoto T, Gandhi TK, Fiskio JM, et al. Development and validation of a clinical prediction rule for angiotensin-converting enzyme inhibitor-induced cough. J Gen Intern Med 2004; 19(6): 684–691.
53. Lyssenko V, Jonsson A, Almgren P, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med 2008; 359: 2220–2232.
54. McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. Br Med J 2006; 332: 1177–1181.
55. Ferrari M, Martignoni E, Blandini F, et al. Association of UDP-glucuronosyltransferase 1A9 polymorphisms with adverse reactions to catechol-O-methyltransferase inhibitors in Parkinson's disease patients. EJCP 2012; 68(11): 1493–1499.
56. Pirmohamed M, Park BK. Genetic susceptibility to adverse drug reactions. Trends Pharmacol Sci 2001; 22(6): 298–305.
57. Steichen, O, Martinez-Almoyna, L, De Broucker T. "Isoniazid induced neuropathy: consider prevention". Revue des maladies respiratoires. Malnutr 2006; 23(2 Pt 1): 157–60.
58. Anonymous.https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5ab01773-d1e4-4b87-884a-9e5b3f13bdcb [Accessed: December 20, 2016].
59. Bushardt RL, Massey EB, Simpson TW, et al. Polypharmacy: misleading, but manageable. Clin Interv Aging. 2008; 3(2): 383–389.
60. Jose J, Jimmy B, Al-Mamari MNS, et al. Knowledge, beliefs and behaviours regarding the adverse effects of medicines in an Omani population. Sultan Qaboos Univ Med J 2015; 15: 234–40.
61. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol. 2004; 57(2): 121–126.
62. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977: 10.
63. Wills S, Brown D. A proposed new means of classifying adverse drug reactions to medicines. Pharm J 1999; 262: 163–5.
64. Aronson JK, Ferner, RE. Joining the DoTS: new approach to classifying adverse drug reactions. Brit Med J 2003; 22; 327(7425): 1222–1225.

65. Singal KC (ed). Proceedings: International workshop on adverse drug reaction monitoring, 3rd Annual conference, Society of Pharmacovigilance, Agra, December (11-13), 2003.
66. Wong GW, Laugerotte A, Wright JM. Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. Cochrane Database Syst Rev 2015; 26; (8): CD007449.
67. Goldstein JN. Should anticoagulation be resumed after intracerebral hemorrhage? Cleve Clin J Med 2010; 77(11): 791–799.
68. Hernández-Díaz S1, Rodríguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000; 160(14): 2093-9.
69. Uher R, Farmer A, Henigsberg N, et al. "Adverse reactions to antidepressants". The Br J Psy 2009; 195(3): 202–210.
70. Gell, PGH, Coombs, RRA. The classification of allergic reactions underlying disease. In Clinical Aspects of Immunology (Coombs, R.R.A. and Gell, P.G.H., eds) Blackwell Science 1963.
71. Bhattacharya S. The facts about penicillin allergy: a review. J Adv Pharm Technol Res 2010; 1(1): 11–17.
72. Vincent PC. Drug-Induced Aplastic Anaemia and Agranulocytosis: Incidence and Mech Drugs 1986; 31: 52-63.
73. Levine B. · Redmond A. Immunochemical Mechanisms of Penicillin Induced Coombs Positivity and Hemolytic Anemia in Man. Int Arch Allergy 1967; 31: 594–606.
74. Benacerraf B, Kabat EA. A quantitative study of the Arthus phenomenon induced passively in the guinea pig. J Immunol 1950; 64: 1-19.
75. McCluskey RT, Benacerraf B, McCluskey JW. Studies on the Specificity of the Cellular Infiltrate in Delayed Hypersensitivity Reactions. J Immunol, 1963; 3: 466-477.
76. Uetrecht J., DJ, Qiang Ma, Idiosyncratic Adverse Drug Reactions: Current Concepts. Pharmacol Rev 2013; 65(2): 779–808.
77. Soliday FK, Conley YP, Henker R. Pseudocholinesterase deficiency: a comprehensive review of genetic, acquired, and drug influences. AANA J. 2010; 78(4): 313-20.
78. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 1991; 324: 169-74.

79. Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Pract Res Clin Haematol 2000; 13(1): 21-38.
80. Whatley SD, Roberts AG, Llewellyn DH, et al. "Non-erythroid form of acute intermittent porphyria caused by promoter and frameshift mutations distant from the coding sequence of exon 1 of the HMBS gene". Hum. Genet 2000; 107(3): 243–8.
81. Lannfelt, L, Wetterberg L, Gellerfors P, et al. (1989). "Mutations in acute intermittent porphyria detected by ELISA measurement of porphobilinogen deaminase". J Clin Chem Clin Biochem. 1989; 27(11): 857–862.
82. Rosenberg H, Davis M, James D, et al. "Malignant hyperthermia". Orphanet J Rare Dis 2007; 2(1): 21.
83. Litman R, Rosenberg H. "Malignant hyperthermia: update on susceptibility testing". JAMA 2005; 293(23): 2918–24.
84. Krause T, Gerbershagen MU, Fiege M, et al."Dantrolene- a review of its pharmacology, therapeutic use and new developments". Anaesthesia 2004; 59(4): 364–73.
85. Rumack B, Matthew H (1975). "Acetaminophen poisoning and toxicity". Pediatrics55(6): 871–76.
86. Heard KJ. "Acetylcysteine for Acetaminophen Poisoning". New Engl J Med 2008; 359(3): 285–92.
87. Anonymous. "Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine".Drug Safety Update (Medicines and Healthcare Products Regulatory Agency (MHRA) 2012; 6 (2): A1.
88. Yassa, Ramzy J, Barry D. "Complications of tardive dyskinesia: A review".Psychosomatics 1985; 26 (4): 305–7, 310, 312–3.
89. Baldessarini, Ross J. "A summary of current knowledge of tardive dyskinesia". L'Encéphale 14 (Spec Issue) 1988; 263–8.
90. Crane, GE. "Rapid reversal of tardive dyskinesia". Am J Psych 1973; 130 (10): 1159.
91. Ross, Colin A, Read, John. "Antipsychotic medication: myths and facts". In Read, John; Mosher, Loren R.; Bentall, Richard P. Models of Madness: Psychological, Social and Biological Approaches to Schizophrenia. London: Brunner-Routledge. 2004: p. 101–14.
92. Rana, AQ, Chaudry, ZM, Blanchet PJ. "New and emerging treatments for symptomatic tardive dyskinesia" (PDF). Drug Design, Dev Ther 2013; 7: 1329–1340.

93. Huang, CC, Wang RI, Hasegawa A, et al. "Reserpine and alpha-methyldopa in the treatment of tardive dyskinesia" (PDF). Psychopharmacol (Berl) 1981; 73(4): 359–362.
94. Caroff SN; Campbell EC, Havey, J, et al. "Treatment of tardive dyskinesia with donepezil: a pilot study". J Clin Psych 2001; 62(10): 772–775.
95. Korsgaard, S. "Baclofen (Lioresal) in the treatment of neuroleptic-induced tardive dyskinesia". Acta Psych Scandinav 1986; 54(1): 17–24.
96. Aia, PG; Revuelta, GJ; Cloud, LJ; Factor, SA (2011). "Tardive Dyskinesia" (PDF).Curr Treat Opt Neurol 2011; 13(3): 231–241.
97. McLaughlin JK, Lipworth L, Chow WH, et al. "Analgesic use and chronic renal failure: a critical review of the epidemiologic literature". Kidney Int 1998; 54(3): 679–86.
98. De Broe ME, Elseviers MM. Analgesic nephropathy. N Engl J Med 1998; 338: 446.
99. Bach PH, Hardy TL. "Relevance of animal models to analgesic-associated renal papillary necrosis in humans". Kidney Int 1985; 28(4): 605–13.
100. Linton AL. "I. Recognition of the problem of analgesic nephropathy". Can Med Assoc J 1972; 107(8): 749–51.
101. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the Q Research and CPRD databases. Br Med J 2015; 350: h2135.
102. Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study. Contraception 2013; 88: 678.
103. Rogers, JM, Kavlock, RJ. "Developmental toxicology". In C.D. Klaassen (ed.):Casarett & Doull's Toxicology, (5th ed.). 1996. pp. 301-331. New York: McGraw-Hill. ISBN 0-07-105476-6.
104. Miller, Marylin T. "Thalidomide Embryopathy: A Model for the Study of Congenital Incomitant Horizontal Strabismus". Transaction of the American Ophthalmol Soc 1991; 81: 623–674.
105. Easton JD. "Potential hazards of hydantoin use". Ann. Intern. Med 1972; 77(6): 998–9.
106. Ausavarat S, Tanpaiboon P, Tongkobpetch S, et al. "Two novel EBP mutations in Conradi–Hünermann–Happle syndrome". Eur J Dermatol 2008; 18(4): 391–3.

107. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991; 324(10): 674-7.
108. Jentink J, Dolk H, Loane MA, Morris JK, et al. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. Br Med J 2010; 341: c6581.
109. Daly S, Mills JL, Molloy AM, et al. "Minimum effective dose of folic acid for food fortification to prevent neural-tube defects". Lancet 1997; 350(9092): 1666–9.
110. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999; 17; 86(3):242-4.
111. Walker BE. Induction of cleft palate in rats with antiinflammatory drugs. Teratol 1971; 4(1): 39-42.
112. Puar TH, Stikkelbroeck NM, Smans LC, et al. Adrenal crisis: still a deadly event in the 21st century. Am J Med 2016; 129(339): e1–e9.
113. Hahner S, Hemmelmann N, Quinkler M, et al. Timelines in the management of adrenal crisis - targets, limits and reality. Clin Endocrinol (Oxf). 2015; 82 (4):497-502.
114. Mehta JL, Lopez LM. Rebound hypertension following abrupt cessation of clonidine and metoprolol. Treatment with labetalol. Arch Intern Med. 1987; 147(2): 389-90.
115. Duncan Js, Shorvon SD, Trimble MR. Withdrawal symptoms from phenytoin, carbamazepine and sodium valproate. J Neurol Neurosurg Psych 1988; 51(7): 924–928.
116. Tandon VR, Mahajan V, Khajuria V, et al. Underreporting of adverse drug reactions: A challenge for pharmacovigilance in India. Ind J Pharmacol 2015; 47: 65–71.
117. Pharmacovigilance program of India (PvPI), NCC, IPC. http://www.ipc.gov.in/PvPI/pv_amcs.html]. [Accessed: January 07, 2017].
118. Venkatraman VJ. Current status of pharmacovigilance in India. Pharmabiz 2015 http://www.pharmabiz.com/PrintArticle.aspx?aid=87506&sid=9. [Accessed: January 7, 2017)
119. Suspected adverse drug reaction reporting form. Central drugs standard control organization. http://cdsco.nic.in/html/ADR_form_PDF_file.pdf [Accessed: January 10, 2017].
120. Naranjo CA, Busto U, Sellars EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharm Ther. 1981; 30: 239–45.

121. Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 2006; 54: 226–33.
122. Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. Ann Pharmacother 2008; 42(7): 1017-25.
123. Sadhotra A, Gupta A, Walia R, et al. Mechanisms, Methods of Detection and Causality Assessment of Adverse Drug Reactions . Ind J Pharm Pharmacol 2016; 3(1): 29-32.
124. Shuka SS, Gidwani B, Pandey R, Rao SP, Singh V, et al. Importance of Pharmacovigilance in Indian Pharmaceutical Industry. Asian J Res Pharm Sci 2012; 2: 4-8.
125. Biswas P, Biswas AK. Setting standards for proactive pharmacovigilance in India: The way forward. Ind J Pharmacol 2007; 39: 124–8.
126. Barnes J. Pharmacovigilance of herbal medicines: a UK perspective. Drug Saf 2003; 26(12): 829-51.
127. Baniasadi S, Habibi M, Haghgoo R et al. Increasing the number of adverse drug reactions reporting: the role of clinical pharmacy residents. Iran J Pharm Res 2014; 13(1): 291-7.