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Drug induced diseases

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Abstract
The Indian pharmaceutical industry is valued at Rs. 90000 crore and is growing at a rate of 12-14% annually. Exports are growing at a rate of 25% compound annual growth rate. The total exports of Pharma products is to extent of Rs. 40000 crore. India has also emerged as a hub for the clinical trials and drug discovery and development. Further more and more drug entities are being introduced which includes new chemical entities, Pharma products, vaccines, dosage forms, and new routes of administration and new therapeutic claims of existing drug moieties. The safe use of medicines is perhaps the single most important criteria that any regulatory authority within a given country has to ensure in order to protect the public health and the integrity of its health care system. Drug induced disease is defined as the unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or to require hospitalization and may persist even after the offending drug has been withdrawn. Drug induced diseases also called as iatrogenic diseases, are well known but least studied entity. In this review, we have collected the information from review and research articles related to the drug induced diseases. This review is intended to aid the understanding of some basic concepts regarding the drug induced diseases. This tends to provide information about the some commonly occurring drug induced disorders, the drugs responsible for inducing disorders, their prevention and some of the treatments.

Keywords: drug induced diseases, adverse effect, unintended drug reactions

Introduction
A drug-induced disease is an unintended effect of a drug, which results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or require hospitalization. Drug-induced disease can result from unanticipated or anticipated drug effects [1]. Public and professional concern about drug induced diseases first arose in the late 19th. In 1922; there was an enquiry into the jaundice associated with the use of SALVARSAN, an organic arsenical used in the treatment of Syphilis. In 1937 in the USA, 107 people died from taking an elixir of sulfanilamide that contained the solvent diethylene glycol. This led to the establishment of the Food and Drug Administration (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed. The major modern catastrophe that changed professional and public opinion towards medicines was the thalidomide tragedy. The thalidomide incident led to a public outcry, to the institution all round the world of drug regulatory authorities, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased awareness of adverse effect of drugs and methods of detecting them. With the adverse reactions some drugs have been withdrawn from use or for some the label has been changed. [1]

2. Types
Diseases caused by drugs or drug induced diseases can be either predictable or unpredictable.
Predictable: Predictable effects are an extension of the normal pharmacological effects of the drug. For example, blood thinners (anticoagulant and anti-platelet drugs) that are used to prevent clotting of blood can cause bleeding as a side effect. Several anti-diabetes medications like insulin and sulfonylureas can cause low blood glucose levels.
Unpredictable: On the other hand, unpredictable effects are completely unrelated to the therapeutic effect of the drug. For example, amiodarone, a drug used to treat abnormal heart rhythms, can cause lung damage. Depending on their severity, drug-induced diseases may be classified as mild, moderate, severe, or lethal if they cause death [2]. Drug-induced diseases can affect various organ systems of the body. Several drugs have been banned because of their ability to cause serious diseases. here are some examples listed below according to the organ system affected [2].
Cardiovascular system: Cardio-toxicity is not restricted to anticancer agents, and almost all therapeutic drug classes have unanticipated cardio-toxicities. However, cardiotoxicity induced by chronically administered drugs, such as neurologic/psychiatric agents and anticancer chemotherapeutic agents, represents a major problem because toxicity may become evident only after long-term accumulation of the drug or its metabolites. Drug-induced cardiotoxicity, commonly in the form of cardiac muscle dysfunction that may progress to heart failure, represents a major adverse effect of some common traditional Antineoplastic agents, e.g., anthracyclines, cyclophosphamide, 5 fluorouracil, taxanes, as well as newer agents such as biological monoclonal antibodies, e.g., trastuzumab, bevacizumab, and nivolumab; tyrosine kinase inhibitors, e.g., sunitinib and nilotinib; antiretroviral drugs, e.g., zidovudine; antidiabetics, e.g., rosiglitazone; as well as some illicit drugs such as alcohol, cocaine, methamphetamine,

ecstasy, and synthetic cannabinoids. Most of the affected patients had no prior manifestation of the disease [3].

Skin: Drug-induced skin disorders are often classified as either acute or chronic. Acute diseases include erythematous eruptions; urticaria, angioedema, and anaphylaxis; fixed-drug eruptions; hypersensitivity syndrome; Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); warfarin-induced skin necrosis; vasculitis; serum sickness–like reaction; acute generalized exanthematous pustulosis (AGEP); and photosensitivity. Chronic disorders include drug-induced lupus, drug-induced acne, and pigmentary changes [4].

Table 1: Types of drug induced skin disorders

Type	Common causative agent
Acute	
Erythomatous eruptions	penicillins, cephalosporins, sulfonamides, anticonvulsants, and allopurinol
Urticaria, angioedema	NSAIDs, antimicrobials, anticancer drugs, ACE inhibitors, corticosteroids.
Fixed-Drug Eruptions	Tetracyclines, barbiturates, sulfonamides, codeine, Carbamazepine, acetaminophen, NSAIDs
Drug Hypersensitivity Syndrome	Allopurinol, sulfonamides, anticonvulsants, Phenytoin
SJS and TEN	Antibacterial sulfonamides, anticonvulsants, nevirapine
Warfarin-Induced Skin Necrosis	Warfarin
Serum Sickness–Like Reactions	Cefaclor, minocycline, penicillin
AGEP	Aminopenicillin, macrolides, quinolones
Photosensitivity	Quinolones, Amiodarone, psoralens, Antineoplastic agents
Chronic	
Drug-Induced Lupus (DIL): Drug-Induced Acne (Acneiform Eruption)	Procainamide, hydralazine, quinidine, Isoniazid, chlorpromazine, TNF inhibitors. Corticosteroids, androgenic hormones, anticonvulsants
Drug-Induced Pigmentary Changes	Minocycline, antimalarials, oral contraceptives, imipramine, anticancer drugs.

Neurological conditions: The term neurologic side effect is commonly used to describe a new drug-induced neurologic syndrome and/or disorder. Changes in the central nervous system (brain, spinal cord) or peripheral nerves can cause a wide variety of symptoms, including loss of coordination and muscle strength, numbness, loss of consciousness, seizures, and paralysis (Table 2) [5].

Table 2: Drug induced neurological conditions

Drug-Induced Disorder	Related Syndromes/Disorders	Adverse Effects
Cerebrovascular disease	Stroke, cerebellar syndrome	Ataxia; dysarthria; nystagmus
Cognitive impairment	Dementia	Confusion; memory loss; decreased ability to concentrate, think, and reason
Delirium	NA	Disturbance in consciousness; impaired cognition
Headache	Medication-overuse headache, intracranial hypertension	Headaches ranging in symptom type (cluster, migraine, generalized)
Nerve and muscle disorders	PN, GBS, neuromuscular blockade, myopathy, demyelination	Muscular weakness, loss of coordination, possible paralysis
Neuroleptic malignant syndrome	NA	Fluctuating heart rate, respiration levels, and level of consciousness
Movement disorders	Akathisia, dystonia, TD, parkinsonism	Tremor; muscular spasms; facial grimacing; tongue protrusion
Optic neuritis, visual disturbances	NA	Loss of visual acuity; color blindness
Seizure disorders	Withdrawal seizures, iatrogenic seizure threshold reduction	Possible loss of consciousness
Serotonin syndrome	NA	Cognitive behavioral changes; autonomic instability; neuromuscular excitability
Sleep disorders	Drug-induced insomnia	Excessive daytime sleepiness; decreased ability to concentrate, think, and reason

Lung: The manifestations of drug-induced pulmonary diseases span the entire spectrum of pathophysiologic conditions of the respiratory tract. As with most drug-induced diseases, the pathological changes are nonspecific. Therefore, the diagnosis is often difficult and, in most cases, is based on exclusion of all other possible causes. Adverse pulmonary reactions are uncommon in the general population but are among the most serious reactions, often requiring intervention. Apnea may be induced by central nervous system depression or respiratory neuromuscular blockade. Although the benzodiazepines are touted as causing less respiratory depression than barbiturates, they may produce a profound additive or synergistic effect when taken in combination with other respiratory depressants. Combining IV diazepam with phenobarbital to stop seizures in

an emergency department frequently results in admissions to an intensive care unit for a short period of assisted mechanical ventilation, regardless of the drug administration rate. Too rapid IV administration of any of the benzodiazepines, even without coadministration of other respiratory depressants, will result in apnea. Epidemiologic studies demonstrate an increase in the prevalence of asthma and COPD with increased use of acetaminophen. The use of aspirin or ibuprofen is not associated with asthma or COPD. Administration of acetaminophen in the first year of life was associated with a 46% increase in risk of asthma symptoms at the age of 6 to 7 years. Bronchoconstriction is the most common drug-induced respiratory problem. Bronchospasm can be induced by a wide variety of drugs through a number of disparate pathophysiologic mechanisms. The frequency of aspirin-induced bronchospasm increases with age, on average at 30 years of age. Both ethylenediamine tetraacetic acid (EDTA) and benzalkonium chloride, used as stabilizing and bacteriostatic agents, respectively, can produce bronchoconstriction. Cough has become a well-recognized side effect of angiotensin-converting enzyme (ACE) inhibitor therapy. According to spontaneous reporting by patients, cough occurs in 1% to 10% of patients receiving ACE inhibitors, with a preponderance of females. [6]

Gastro-intestinal tract: Medication-induced gastrointestinal (GI) symptoms and endoscopic pathology are commonly encountered in clinical practice. Medication-induced GI disorders may closely mimic other GI conditions (eg, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)), and failure to recognise drug-related symptoms may lead to unnecessary investigations and treatment. Medications produce symptoms by altering GI physiology (eg, constipation induced by anticholinergic medication), by causing tissue toxicity and damage (eg, ulcers from non-steroidal anti-inflammatory drugs (NSAIDs)), by changing the intestinal microbiota (eg, antibiotics causing *Clostridium difficile* infection), or by unknown mechanisms, such as with metformin. The pharmacologically active compound, as well as the excipient (or packaging) of the tablet or capsule can cause problems. Nausea and vomiting may be caused by mechanisms remote from the GI tract [7, 2].

Table 3: Drugs which causes GIT adverse effects

Conditions	Drug responsible
Dyspepsia	Taxanes, NSAIDs
Acute esophagitis	Tetracyclines, bisphosphates.
Reactive gastropathy	NSAIDs
Peptic ulcer	NSAIDs, corticosteroids
Granulomatous (in stomach)	Lanthanum carbonate
Acute gastritis	Resins
IBD	Rituximab, TNF inhibitors, NSAIDs
Colitis	Sodium phosphate, PPI's, statins, colchicines
Ischemia	Digitalis, ergotamine, cocaine, oxygen peroxide.

Kidney: Drug-induced nephrotoxicity is a common problem in clinical medicine and the incidence of drug-related acute kidney injury (AKI) may be as high as 60 percent. Drugs can cause nephrotoxicity by altering intraglomeu- lar hemodynamics and decreasing GFR (ACEI, angiotensin-converting enzyme blockers [ARBs], NSAID, cyclo- sporine, and tacrolimus). Certain drugs such as ampicillin, ciprofloxacin, sulfon- amides, acyclovir, ganciclovir, methotrexate and triam- terene are associated with crystal nephropathy. Statins and alcohol may induce rhabdomyolysis because of a toxic effect on myocyte function. Drugs associated with tubular cell toxicity and acute in- terstitial nephropathy include aminoglycosides, ampho- tericin B, cisplatin, beta lactams, quinolones, rifampin, sulfonamides, vancomycin, acyclovir, and contrast agents. Chronic use of acetaminophen, aspirin, di- uretics and lithium is associated with chronic interstitial nephritis leading to fibrosis and renal scarring [8].

Blood: The incidence of idiosyncratic drug-induced hematologic disorders varies depending on the condition and the associated drug. Few epidemiologic studies have evaluated the actual incidence of these adverse reactions, but these reactions appear to be rare. Drugs can produce anaemia by reducing the production of red blood cells by the bone marrow (e.g. chloramphenicol, sulfonamides and carbamazepine), or destroying the formed red blood cells by a process called hemolysis (e.g. primaquine, penicillin and sulfonamides). Hemolysis is particularly a problem in patients with the deficiency of an enzyme called glucose-6-phosphatase. Some drugs reduce white blood cell counts and increase the chances of suffering from infections. These include methimazole, phenylbutazone and clozapine. Heparin has been associated with thrombocytopenia, a condition that lowers the platelet counts in the blood and increases the chances of bleeding [9].

Bone: Drugs can cause accelerated bone loss as well as disturbances in serum calcium levels. Long-term use of glucocorticoids can weaken bones causing osteoporosis and increasing the risk of fractures. The anti-tubercular drugs ethambutol and pyrazinamide can increase the blood uric acid, causing a gout-like disease [10].

3. Diagnosis of DIDs

Drug-induced diseases are primarily diagnosed based on the history of drug intake obtained from the patient or the family. The symptoms should appear at a reasonable time frame after taking the medication. By default, physicians should enquire about drug intake to any patient coming to the clinic with a problem so as not to miss out on a drug-induced disease. If the drug is re-administered the symptoms may reappear. This is referred to as re-challenge. Re-challenge confirms a drug-induced disease, but is usually not done due to ethical reasons [2].

4. Treatment of DIDs: The first step in the treatment of drug-induced diseases is to report the adverse effect to the physician who may stop the intake of the medication or at times, reduce the dose gradually, and replace with an appropriate alternative. Many times, this simple step can relieve the patient of the symptoms. Those who do not recover require additional treatments depending on the adverse event [2].

5. Prevention of DIDs

Steps that could help to prevent a drug-induced disease include the following:

- Always inform your doctor if you suffer from any illness or take any other medication including a nutritional supplement before you are prescribed a medication.
- Inform your doctor if you have suffered from any previous allergic reaction to a drug or any other substances like food ingredients.
- Take the medication only as prescribed by the doctor. Stick to the dose, duration of treatment as well as other instructions like taking it after meals [2].

6. Conclusion

Iatrogenic disease or drug induced disease (DID) is an ever enduring concern for patients, healthcare professionals and health administrators. In spite of being a major concern in clinical practice, DID has not been given the due attention it deserves. One of the reasons for this may be that DID causes apprehension among health care professionals making them uncomfortable as well as unwilling to be part of studies undertaken to reduce DID. In India, several individual case reports have been published related to specific iatrogenic disease but a comprehensive study on this problem is not yet published. The true incidence or prevalence of DID in our country is not known.

The magnitude of adverse drug reactions which includes DID is huge. Considering its importance, the Central Drugs Standard Control Organization (CDSCO), New Delhi, Government of India, had initiated a nation-wide pharmacovigilance programme of India (PvPI) in July 2010. The total number of Individual Case Safety Reports (ICSR) in PvPI database is 84,470. In the US, it was reported that ADRs accounts for more than one lakh death each year and it is between the fourth and sixth leading cause of death. In our country, we do not have statistics on DID but the total ADRs in PvPI database for the last few years are less than one lakh. This indicates the scenario of under reporting of ADRs in our country compared to United States of America.

The various factors contributing to DID can be related to pharmacokinetic and pharmacodynamic of drugs, non-adherence to prescribed drug therapy as well as medication errors. Concurrent diseases (e.g. liver and renal impairments), genetic polymorphisms in drug metabolizing enzymes and transporters, nutritional factors (hypo-albuminaemia may result in more free drug of highly protein bound drugs) and concomitantly administered drugs may also contribute to alteration in drug metabolism as well as target receptor activities of drugs. Hence in this era of personalized medicine, prescribers need to understand and update their knowledge on the rapidly transforming drug information. The acquaintance of pharmacokinetic and pharmacodynamic knowledge of a drug can help to prevent the DID. Moreover, a good understanding of pharmaceutical formulations and their applications can help in reducing DID.

Being on the front lines of patient care as well as pharmacotherapy, healthcare professionals need to be knowledgeable regarding the risk of drug-induced diseases, including methods of detection, prevention, and management. To be more efficient, health care practitioners need to be skillful in patient consultation and education in addition to possessing knowledge on complex biomedical science.

The WHO -UMC (Uppsala Monitoring Centre) Global drug safety database for the year 2013 has 8.5 million ADR reports. In this, India's contribution accounts for nearly 0.7 per cent of the global data base. In the last 30 years, India has witnessed banning or withdrawal of nearly 90 drugs for manufacture and sale by CDSCO (Central Drugs Standard Control Organization). This forecasts the urgent need to expand the countrywide PvPI activities so as to implement safety decisions and policy at the regulatory levels in the interest of patient safety. Policy decisions regarding patient safety and medication errors can be achieved through promotion of population based surveillance of DIDs by PvPI in association with CDSCO. In addition, continuing medical educational programmes and training need to be imparted on the healthcare professionals to keep them updated about DIDs as well as on the measures taken to prevent them. The importance of spontaneous reporting of adverse drug reaction needs to be included in the curriculum of all healthcare professionals and the habit needs to be cultivated right from the undergraduate level. While doing so care should be taken to maintain confidentiality of the patients as well as reporting personals so as to encourage further reporting. Likewise during diagnosis as well as while teaching medical graduates, emphasis needs to be given on deliberation of DID as one of the causes of the disease. Basic and epidemiological researchers interested in evidence based medicine and personalized medicine can be motivated to contribute towards the detection, quantification and reduction of DIDs of the marketed drugs. In addition, carrying out systematic reviews as well as meta-analysis to generate evidence towards the occurrence of DID can add required information to the armamentarium of pharmacovigilance.

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