Drug induced diseases and teratogenicity: An update

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Abstract:

Drug-induced disorders often known as iatrogenic diseases, are a well-known yet understudied phenomena. Various chronic conditions, multiple physicians, hospitalisation, medical or surgical operations, long-term medicine use, advancing age, female sex, and a specific class of pharmaceuticals are all risk factors for drug induced diseases. As a result, in this era of customised medicine, prescribers must comprehend and keep up with quickly changing pharmacological information. Teratogenicity is defined as the occurrence of congenital malformations and their causes as a result of teratogenic agents like some viral, spirochetal, and protozoal infections, physical agents like ionising radiations and excessive heat, and pharmacological drugs like thalidomide, excessive vitamin A, corticosteroids, antiepileptic, antimalarial, anti-leishmaniasis, and antihypertensive drugs. The prevalence of congenital birth defects ranges from 2 to 5% in the first year following delivery.

Keywords: *drug induced diseases, iatrogenic diseases, adverse drug reactions, teratogenicity and teratogenic agents.*

Introduction:

A drug-induced sickness is an unwanted and unforeseen side effect of a medication that causes death or morbidity with symptoms severe enough to necessitate medical care and/or hospitalisation. Pharmacological-induced disease can be caused by undiscovered or well-understood drug side effects.

Drug therapy during pregnancy is a major source of concern due to the risk of teratogenic consequences and physiologic changes in the mother because of the pregnancy. The pharmacokinetics of medications taken are affected by pregnant physiology, and certain drugs can reach the foetus and cause harm. Historical events like as the thalidomide crisis in the 1960s and the teratogenic effects linked to the use of diethyl-stilboestrol in 1971 have influenced the debate over drug usage during pregnancy and lactation. Following these incidents, the US Food and Drug Administration enacted tight laws governing treatment labelling and the use of drugs during pregnancy, demanding demonstrations of a drug's safety and efficacy before it can be sold commercially.In this review article we are going to review about the various drugs induced disease in all the major system of the body along with the mechanism of disease caused by drugs and drug induced teratogenicity [1].

Types:

Drug-induced disorders can be classified as Type 1 (predictable/expected) or Type 2 (unpredictable/unexpected). The drug's predictable or predicted side effects are an extension of the drug's usual pharmacological effects. Blood thinners (anticoagulant and antiplatelet medications, for example) can cause bleeding as a side effect. Low blood glucose levels can be caused by several anti-diabetes drugs, including insulin and sulfonylureas.

Unpredictable consequences, on the other hand, have nothing to do with the drug's therapeutic function. Amiodarone, for example, a medicine used to treat irregular heart rhythms, can harm the lungs. Drug-induced disorders are classed as mild, moderate, severe, or deadly if they result in death, depending on their severity [2]. Drug-induced disorders can impact the body's many organ systems. Several medications have been outlawed due of their potential to cause serious illnesses. Following are some examples of organ systems that have been compromised [2].

Gastrointestinal system:

In clinical practise, medication-induced gastrointestinal symptoms and endoscopic pathology are prevalent. Irritable bowel syndrome and inflammatory bowel diseases are examples of GI disorders that can be caused by medication. Drug causes symptoms via modifying GI physiology (e.g., anticholinergic medication causes constipation, NSAIDs cause ulcers), influencing the intestinal microbiota (e.g., antibiotics cause Clostridium difficile infection), or by an unknown mechanism (e.g., metformin causes diabetes). Nausea and vomiting can be triggered by mechanisms that are not related to the gastrointestinal tract [3]. Drug-induced gastrointestinal system-based disorders are discussed in Table 1.

Excretory system:

Currently, the entire population is exposed to a variety of pharmacological drugs, the majority of which are harmful and prescribed without scientific backing. Given that the kidney excretes

the majority of the drug, it's logical to believe that the kidney could be a special target for their hazardous effects. Immune-related toxic effects, analgesic neuropathy, drug-induced glomerular diseases, the direct toxic effects of the drugs, nephrogenic system fibrosis, selective toxic effects, renal hemodynamics related renal failure, and crystalline neuropathy will be presented according to their pathophysiologic mechanisms [4]. Table 2 shows the effects of drugs on the excretory system.

Table 1. Drug-induced gastrointestinal system-based diseases

Disease	**Drug causing**	**Mechanism**
Oesophagitis	Tetracycline, bisphosphonate, Potassium chloride, NSAIDs, Iron	Due to mucosal injury
Gastroesophageal Reflux	Nitrates, Calcium channel antagonists Dopaminergic agents, anticholinergic drugs Progesterone, Methylxanthine	Alter lower oesophageal sphincter pressure
Dysphagia	Anti-psychotic drugs, Alcohol	Inhibit striated muscle function
	Anticholinergic drugs, Calcium channel blocker, Theophylline	Inhibit smooth muscle function
Nausea and vomiting	Potassium chloride, NSAIDs, Iron	Cause tissue damage
	Digoxin, Dopaminergic agent, Opiates, Chemotherapeutic agent	Act via chemoreceptor in central nervous system
Constipation	Nifedipine	Inhibition of colonic motor activity

Table 2. Drug-induced excretory system-based diseases

Disease	**Drug causing**	**Mechanism**
Kidney failure	Cocaine, MDMA	Due to rhabdomyolysis
	inhalant	Renal tubular acidosis
	heroine	Amyloidosis
Functional renal failure	Estroprogestins, diuretics	Platelets aggregation, Thrombotic microangiopathy
Analgesic neuropathy	phenacetin	Chronic interstitial diseases and neuropathy
Glomerular diseases	Alpha methyl dopa, Penicillamine Interferone, Levamisole, procainamide	By affecting immune system
Chronic interstitial nephritis	Herbal medications,exoticunlicenced or OTC drug	Interstitial fibrosis
Renal impairment	Cisplatin, iphosphamide	Intracellular hydroxyl radical formation
AIN neuropathy	NSAIDs	Hapten mediated immune mechanism

	Methicillin, Penicillin, H-pump inhibitor	Other immune mechanism (IC disease ,anti tubule basement membrane antibodies
Prerenal azotemia	PG inhibitor, ACE-Sartans	Afferent arterioles constriction and efferent arterioles dilation
Obstructive intratubular ARF	HAART drugs, Triamterene Sulfa drugs, Uricosuric drugs	Intratubular precipitation of drugs and urine components (uric acid and others)
Acute glomerulo nephritis	Penicillin	Glomerular injury
	Cephalosporin	Glomerular + interstitial injury
Acute renal failure	Massive infusion of mannitol,glycerol dextran	Osmotic swelling of proximal tubular cell

Endocrine system:

Drugs can cause endocrine problems through a variety of ways, including direct changes in hormone production, changes in hormonal axis regulation, effects on hormonal transport, binding, and signalling, and changes in counter-regulatory hormone systems. Drugs can have a significant impact on the assessment of endocrine parameters by interfering with diagnostic testing. Drug-induced endocrine and metabolic issues include glucose metabolism problems, electrolyte and calcium imbalances, and thyroid and gonadal dysfunction. Understanding the proposed mechanism of these drug effects, as well as their evaluation and differential diagnosis, may help with critical interpretation of clinical observations related to these disorders, better prediction of drug-induced adverse effects, and better treatment choices and rationales [5,6,7,8]. Drug-induced endocrine system-based disorders are discussed in Table 3.

Table 3. Drug induced endocrine system-based diseases

Disease	**Drug causing**	**Mechanism**
suppression of TSH	Hydrocortisone Prednisolone	The glucocorticoid receptor is activated. TRH synthesis/secretion inhibition
	Dopamine agonists	On thyrotropes, dopamine receptors (D2) are activated. TSH pulse amplitude is reduced.
	Somatostatin analogs	Somatostatin receptors in thyrotropes are activated. TSH secretion is inhibited. Thyroid hormone metabolism may have been changed.
Hyperprolactine mia	verapamil, methyldopa, tramadol, buprenorphine, methadone	The concentration of PRL in the blood is moderately elevated.

	estrogen-containing oral contraceptives	Moderate hyperprolactinemia is frequently caused by the powerful oestrogen ethynylestradiol.
	dopamine receptor antagonists	PRL concentrations in the blood are highly raised, and in some cases can exceed 200 g/L.
	Promethazine (phenothiazine derivative),domperidone, Metcopromide	serum PRL concentrations are significantly elevated
Thyroiditis	pembrolizumab	circulating CD56, CD16 and NK cells
Grave's disease	cancer immunotherapy, alemtuzumab	Not known
Thyroid disfunction	gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib	Tyrosine kinase inhibitors
Hypothyroidism	Carbamazepine,topiramate , levetiracetam Amiodarone	T3 and T4 metabolism should be increased. Due to a feedback mechanism, the activity of type 2 5′-deiodinase enzyme in the pituitary is inhibited. Thyroid hormone transport across the plasma membrane is inhibited, preventing T4 and T3 from entering peripheral tissue.
Serotonin syndrome	serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), as well as monoamine oxidase inhibitors (MOI)	By blocking the catalytic enzyme monoamine oxidase, it slows down the breakdown of 5-HT.
Bone and calcium metabolism deregulation	Antiepileptics (carbamazepine, phenobarbital, phenytoin and primidone)	Cytochrome 450 inducer and PXR activator.
	Antiretroviral therapy (abacivir,lamivudine,zidovudine and didanosine)	Activate PXR , alter vitaminD metabolism,
Hypocalemia	Antineoplastics(doxorubicin , cytarabin,vinblastin)	Not known
	glucocorticoids	Reduce the expression of CYP27B1, while increasing the expression of CYP3A1 and

		CYP24A1, the two most important enzymes in vitamin D deterioration.
Obesity	Long acting insulin, sulfonylurea ,maglinitide	Increased subcutaneous fat and fluid retention
Hyperglycemia	glucocorticoids	Insulin resistance is a problem, but so is -cell function and insulin secretion, especially at higher doses.
	Diuretics ,betablockers	Impaired insulin release from β-cell.
	Somatostatin analogs	inhibiting insulin and glucagon secretion
	Atorvastatin ,rousavastatin	Many glucoregulatory mechanisms are disrupted, resulting in reduced insulin secretion and action.
Ejaculation dysfunction	Antipsychotic , antidepressants , opoids and cannabis	increased serotonin has a central influence on the hypothalamus, mild elevation of PRL, and maybe a direct action on smooth muscle cells.
	Chemotherapeutic agents (mustine,cisplatin)	induce irreparable damage to germ cells and the seminiferous epithelium by crossing the blood-testis barrier
Sexual dysfunction	Paracetamol	Prostaglandins, which are important for sperm fertilisation, should be reduced.
	Metoclopramide	Increase PRL level
	Antihypertensives	drop in pressure and the potential for net hydraulic effects on erection
	Statins	T levels drop as steroidogenesis substrates are depleted, and sperm membranes, which are particularly high in cholesterol, are disrupted.

Cardiovascular system:

There are many drugs that used to treat cardiovascular disease and cause toxicity. The most common of them are cardiac arrhythmia caused by digitalis and toxic level of other antiarrhythmic drugs include quinidine, procainamide and phenytoin. There are various toxic effects in the cardiovascular system due to drugs that are not used in cardiac treatment but they are not widely known like sensitivity towards thromboembolism for women taking oral contraceptives. There are many anticancerous drugs that cause cardiac toxicity exemplified by cardiomyopathy caused by doxorubicin and daunorubicin. Many antipsychotic drugs and antidepressant drugs like phenothiazine can cause arrhythmia [9,10]. Here in **table 4** drug-induced cardiovascular system-based diseases are mentioned.

Table 4. Drug induced cardiovascular system-based diseases

Disease	Drug causing	Mechanism
Arrthymia	Digitalis Quinidine Procainamide Phenytoin	Alteration in impulse formation and conduction. Quinidine shortens the A-V conduction time,prolong Q-T interval. Delay in diffuse intraventricular conduction Impair left ventricular myocardial function.
Bradycardia	Beta blockers	Impairement of beta adernoreceptor stimulation
Hypertension	Prednisone Oral contraceptive	Alter sodium retaining ability. Elevated level of plasma angiotensin-II
Hypotension	Phenothiazine	Alpha adernoreceptor blocking effect.
Thrombophlebitisand venous thrombosis	Oral Contraceptive	Increase in prothrombin and clotting factor VII IX and X
Cardiac myopathy	Doxorubicin Lithium	Damage myocardial DNA prevent repair and leads to cell death. Intracellular potassium is replaced by lithium influx.
Cardiac ischemia	Sympathomimetic amines	Vary degree of cardiac ionotropic andchronotropic stimulation
Electrocardiogram abnormality	Phenothiazine	S-T segment depression, prolongation of Q-T nterval.

Respiratory system:

There are many drugs that produce adverse pulmonary effect that are similar to agents from same pharmacological activity, like angiotensin-converting enzyme cause cough and beta blockers caused bronchospasm or NSAIDS and eoisinophilic Pneumonia, previous studies try to quantify the frequency of drug induced adverse pulmonary reaction, but thry are limited by inconsistencies by limited Patient study [11,12,13]. Here in **table 5** drug induced respiratory system-based diseases are mentioned.

Table 5. Drug induced respiratory system-based diseases

Disease	Drug causing	Mechanism
Apnea	Benzodiazepine Barbiturates Midazolam	Frequent use of inhibitors of cytochrome P450 with benzodiazepine increase risk of cardiac depression
Asthma	Acetaminophen	It reducethye level of glutathione in airway epithelium that lead to oxidant damage in lungs

Aspirin inducedasthma	aspirin	Cox inhibition thus producuction of leukotriene C4 D4 increases that promote histamine release
Alveolar hemorrhage	gefitinib	Express ant (3)
Bronchospasm	Beta blockers	Increase bronchiobstruction and airway activity
Systemic lupus erythematosus	phenytoin Procainamide	Inhibition of DNA methylation, the demethylation of CD4 cell make them autoreactive[1]
Eosinophilic reaction	Diltiazem Daptomycin	Drug accumulation near epithelial alveolar surface and pneumonia.
Hypersenstivity Pneumonitis	Methotrexate	-
Bronchiolitis Obliterans	Sulfasalazine Pencillamine	-
Fibrosis and Pneumonitis	Bleomycin	Stimulate production of Pulmonary antioxidant enzyme

Skin and bone diseases:

Drug-induced skin diseases are frequently divided into two categories: acute and chronic. In acute category Erythematous eruptions, Stevens-Johnson syndrome, urticaria, serum sickness–like reaction, angioedema, hypersensitivity syndrome and warfarin anaphylaxis are mainly belonged. In chronic skin diseases category drug induced lupus and acne, and pigmentary alterations are exemplified [14].

Drugs can hasten bone loss and cause calcium levels in the blood to fluctuate. Long-term glucocorticoid use can weaken bones, leading to osteoporosis and increased fracture risk. Ethambutol and pyrazinamide, antitubercular medicines, can raise blood uric acid levels, causing gout-like symptoms [15].

Teratogenicity:

Because the physiology of pregnancy alters the pharmacokinetics of medications administered, and certain pharmaceuticals can reach the foetus and cause harm, pregnancy is a unique physiological event in which drug therapy poses a significant risk. It is impossible and maybe unsafe to completely forego pharmaceutical treatment during pregnancy because many women have medical issues that require continuous and episodic care when they become pregnant (e.g. asthma, epilepsy, hypertension). During pregnancy, new medical problems can occur, and existing ones can worsen (for example, migraines and headaches), necessitating pharmacological intervention. Some teratogenicity-causing drugs and their mechanisms of action are outlined (table 6) [16-22].

Table 5. Drug induced teratogenicity

Drug	Mechanism of action/ Effects
Asprin	Delay in the onset of labour, premature closure of the ductus arteriosus, jaundice, and foetal brain damage
Tetracycline	Increased susceptibility to cavities in the body, slowed bone growth, and persistent yellowing of the teeth
Kanamycin	Damage to the fetus's ear causes deafness (risk of ototoxicity)
Carbamazepine	Damages DNA and has been linked to craniofacial abnormalities, IQ abnormalities, and growth retardation.
Phenobarbital	While macroscopically, this creates free radicals and DNA base transversion, it also causes poor growth, motor development, and foetal death.
Tpoiramate	Hypospadias and oral clefts in neonates are connected.
Warfarin	Vitamin K antagonists impede -carboxylation of glutamyl residues, lowering protein-calcium binding capacity. The skeletal anomalies could be explained by this suppression throughout foetal development.
Vitamin a	High doses of Vitamin A in pregnant rats caused neural tube defects, for instance, exencephaly, spina bifida with meningocele, hydrocephalus, eye malformations, and cleft palate
Maternal smoking	Birth weight is reduced. Heart, brain, and face birth abnormalities are also more likely in smokers' children.

Diagnosis:

Drug-induced diseases are primarily diagnosed based on the patient's or family's drug consumption history. After taking the drug, the symptoms should develop within an acceptable amount of time. To avoid missing a drug-induced disease, clinicians should ask about drug intake to any patient who comes to the clinic with a problem. Symptoms may recur if the medicine is re-administered. Re-challenge is the term for this. Re-challenge establishes the presence of a drug-induced disease; however, it is rarely done for ethical reasons.

Treatment:

The first step in treating drug-induced diseases is to notify a physician, who may decide to cease taking the medicine or, in some cases, gradually reduce the dose and replace it with a suitable alternative. This easy step can often alleviate the patient's problems. Those who do not recover may need extra therapy, depending on the severity of the adverse event.

In July 2010, the Central Drugs Standard Control Organization (CDSCO), New Delhi, Government of India, launched a national pharmacovigilance programme of India (PvPI) in recognition of its relevance. In the PvPI database, there are 84,470 Individual Case Safety Reports (ICSR). ADRs are considered to be the fourth to sixth major cause of death in the United States, accounting for more than one lakh deaths each year. We do not have DID numbers in our country, but the total ADRs in the PvPI database for the last few years is fewer

than one lakh. This illustrates our country's underreporting of ADRs in comparison to the United States of America.

Conclusion:

Patients, healthcare providers, and health administrators are all concerned about drug-induced disease. Despite the fact that it is a substantial challenge in clinical practise, it has not gotten the attention it needs. One reason for this could be that DID makes health care professionals nervous, making them uncomfortable and unwilling to participate in studies aimed at reducing DID. Several case reports on certain iatrogenic diseases have been published in India, but a complete study on the subject has yet to be published. In our country, the exact frequency or prevalence of DID is unknown.

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