Review Article

An Overview: Drug Induced Diseases

Mahima K.V.[1*], Ashish Kumar[1], Asheesh Kumar Gupta[2]

[1] N.E.T. Pharmacy College, Raichur, Karnataka, India, 584101*
[2] Dept. of Pharmacology, U.I.P.S., Uttaranchal University, Dehradun, Uttarakhand, India

ABSTRACT

Drug induced disease is a major concern for patient, healthcare professionals and health care administrators. Several case reports have been published related to specific iatrogenic disease but a comprehensive study of this problem is not yet published. In our country true incidence or prevalence of drug induced disease is not known. It flags an important issue which needs attention. 99.3% of total drug induced diseases were reported as type A reactions. Health care professional should have knowledge regarding the risk about drug induced diseases. Cardiotoxicity and hepatotoxicity is a common side effect of many drugs. 5- fluorouracil and cyclophosphamide and other anticancer drugs mainly anthracyclins causes cardiotoxicity. Complication associated with these drugs cause hypoxia, coronary ischemia, calcium overload, contractile dysfunction and cardiomyopathy. Drug that increase the risk of drug induced hypersensitivity reactions are : (1) molecular weight > 4000 Da ,(insulin, erythropoietin) , (2) the ability of parent drug or its active metabolite to bind to a carrier protein and form a complete antigen, (3) presence of foreign protein or large polypeptides of nonhuman origin (streptokinase, beef or pork insulin). Possible drug induced disorder is needed to avoid potentially serious and/ or fatal drug rechallenges.

Key words: *Iatrogenic disease, Drug induced disease, Drug side effects, Adverse drug effects*

Corresponding Author: Mahima K.V, H.No: 11-10-84, Bresthwarpet, Near Geetha Mandir, Raichur, Karnataka, India. 584101, Ph: 8884676007
E.mail: kuramahima@gmail.com

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INTRODUCTION

Drug-induced diseases (DIDs) are well known but least studied. The magnitude of adverse drug reactions which includes DID is huge. A drug induce disease is the unintended effect of a drug, which results in mortality and morbidity of a patient. Unanticipated or anticipated drug effects can be result from drug induced disease. 3-5% of hospital admissions are caused by ADR.[35] 0.32%- 6% incidence of fatal and serious adverse reaction in hospital patient has been reported. Drugs can have undesirable effects on organs throughout the body. Cardiac disease: Cardiac failure particularly congestive cardiac failure can alter the pharmacokinetic properties of drug. Carddio-toxicity accounted for 45% all drugs withdrawn between 1994 to 2016 which is mainly due to cardiac ischemia and arrythmogenic effect. Cyto-toxicity induced- chemotherapy cardiotoxicity has a high incidence.[31,32]

Ear disorder: Potential ototoxicity of some antibiotics was recognized after world war-II by health professionals. Due to the drugs damage of various auditory system in different ways-tinnitus, hearing loss, hyperacusis, aura fullness, dizziness, vertigo.[37] Ototoxic drugs can act on cochlea or vestibular system or both. Ototoxicity occurs in all age groups.

Eye disorder: Several different drugs have the potential to cause the elevation of intraocular pressure. Dietary supplements have also been reported to induce the open angle glaucoma. Drug-induced kerato-conjunctival disorders present mainly as conjunctival hyperaemia (red eye), with or without superficial involvement of corneal involvement. Drug preservative in ocular medication causes these adverse effects. Cloudiness of the lens due to toxic effect of drugs. Uveal tract disease, glaucoma, cataracts, retinal abnormalities, optic nerve disease can be caused by drugs toxic effect.[36]

GIT disorder: Drug induced git disorder such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) can be mimic by drugs. The adverse gastrointestinal effects of some medications, such as non-steroidal anti-inflammatory drugs are well established, other commonly prescribed drugs, such as antipsychotics, antidepressants and metformin are less well understood and warrant further study. Gastric disorder or oesophegeal disorders mainly occur due to over the counter drug intake. Digoxin, opiate, chemotherapeutic agents, dopaminergic agents cause nausea vomiting via chemoreceptor in central nervous system.[38] NSAID, potassium chloride, iron cause the effect via tissue damage. Drug-induced colitis is an important problem, with antibiotics the commonest drug cause.Strategies to minimize the adverse GI effects of drugs include giving the lowest dose of NSAID for the shortest time, selective COX-2 inhibitors for high-GI/low-cardiovascular risk patients, and upper GI mucosal protection by co-prescription of NSAIDs with proton pump inhibitors.[39]

DRUG INDUCED EYE DISEASES:

Every drug seems to affect various parts of tissues and its functions. Many people are actually unaware of vast adverse drug effects which finally affects our most crucial organ i,e., eyes. Some of the common eye diseases which are reported frequently includes, diabetic retinopathy (ranks first), due to increased diabetes among the population, glaucoma(ranks second), age-related macular degeneration(AMD). ranks third among global. Other diseases or conditions such as, cataracts, ocular hypertension, uveitis, abnormal eye movement, dry eyes, bulging eyes, eye flashes, mydriasis, miosis, cycloplegia, central retinal vein occlusion etc.Some of the manifestations include hypersensitivity reactions, dermatitis, and inflammation. There are many drugs that cause damage to the multiple parts of eyes. The eyelids, conjunctiva (a thin mucous membrane that covers inner part of eyelids and front of an eye), and outer part of cornea are the common targets for drug toxicity. Diabetic retinopathy is a condition in which a persistent elevation in blood sugar levels that occurs with diabetes, which damages the capillaries of retina, which supplies the oxygen and nutrition to the cells. Hence, the drugs which cause elevation in the blood glucose levels, should be strictly avoided.

E.g:- Corticosteroids (hydrocortisone, prednisone) which are used to treat inflammatory diseases like rheumatoid arthritis, lupus, or any allergies. Statins, which are used to lower the cholesterol levels in the body. Isotretinoin is used for treating the acne condition. Beta-blockers and thiazide diuretics which are used in hypertension condition, drugs used to treat anxiety depression, mental health such as clozapine, olanzapine,

risperidone etc., can elevate the blood sugar levels, which is a risk factor for diabetic retinopathy.

Retina acts like a film, senses the light on to its surface, transforming into electric signals. The toxic substances can reach retina through blood, leading to visual disturbances. Other abnormalities are caused by,

Table No.-1. Drugs and their adverse effects

Drugs	Adverse Effects
Chloroquine and hydrochloroquine	Retinal damage
Antipsychotic drugs (Chlorpromazine, Thioridazine)	Cataract, Blurred vision, loss of night blindness.
Tamoxifin	Retinal damage, reduced colour vision, deposition of crystals in retina.
Isotretinoin	Blind vision

Uvea is the pigmented layer consisting of iris, choroid and ciliary body. Uveitis is an inflammation of uvea. The mechanism in drug induced uveitis is not clear. Moxifloxacin is a broad spectrum antibiotic belongs to the class of fluoroquinolones, which inhibits DNA-gyrase and DNA topoisomerase. There exist a few cases on moxifloxacin induced. A female patient of age 54years, after the therapy with moxifloxacin, presented with bilateral anterior uveitis associated with pigment dispersion syndrome and iris trans-illumination. The mechanism of inducing is not clear. But, Uveitis is associated with Autoimmune predisposition, phototoxicity, or a viral infection It is the first report in Latin America.[2] Systemic use of sulphonamide derivatives reported to have drug induced uveitis. 12 of 24 patients were treated with co-trimoxazole. 6 reports included ocular symmetry with all patients having bilary inflammation. 7 patients experienced adverse effects within 8 days of co-trimoxazole therapy and 3 have rechallenge history. The clinical menifestations found are, SJS, macular rashes stomatitis, granulomatous hepatitis.[3]

Bisphosphates are used to treat osteoporosis. Several medicines in this class are associated with uveitis. Pamidronate sodium IV is mostly associated with ocular side effects. Common clinical manifestation includes conjunctivitis, scleritis, episcleritis. In 1993, 23 cases were reported by the Ciba-Geigy Central Epidemiology and Drug Safety Center, in which, 57% had non-specific conjunctivitis, 30% had anterior uveitis, 13% had scleritis or episcleritis, and also positive rechallenge occurred in 73% cases. In an old 68years old woman, who was treated with clodronate for postmenopausal osteoporosis. The patient presented with history of spinal pain since 3 months. Treated with clodronate 300mg once weekly IM. After 3 months, the patient started to report symptoms of uveitis such as ocular redness, photophobia, transient tears etc. Positive rechallenge is seen .Hence uveitis is related to clodronate is confirmed. Glaucoma is an ocular disorder that leads to an optic neuropathy characterized by increased intraocular pressure,changes in optic nerve head finally associated with vision loss.

Table No.-2. The drugs which potentiates the increased intraocular pressure are-

Open-angle glaucoma:	Eg: Ophthalmic corticosteroids(high risk), systemic/nasal corticosteroids, Ophthalmic anticholinergics, vasodilators(low risk), Cimetidine (low risk)
Closed-angle glaucoma:	Eg: Topical anticholinergics, antidepressants, topical sympathomimetics, ipratropium, antihistamines, benzodiazepines (low risk)

Steroids are the anti-inflammatory drugs which are generally used to treat ocular and systemic conditions. Cataract and glaucoma are the common side effects. Chronic administration of steroids (eye drops), may cause rise in IOP and optic neuropathy, finally leads to an avoidable irreversible blindness. Some controversial issues caused by steroidal use are: Optic neuritis, Thyroid ophthalmopathy and complications related to eyes such as, Posterior subcapsular cataract, glaucoma etc. [4] Dexamethasone causes more frequently in rise in IOP, than compared to prednisolone and hydrocortisone. Their found a significant increase in IOP after 0.1% dexamethasone drops three times a day for 4 weeks is administered in the patient.

Table No.-3. Drug induced glaucoma

Name of the drug	Type of glaucoma
Acetazolamide	Narrow-angle, Lens swelling
Anticancer drugs: docetaxel, imatinib, paclitaxel.	Open angle glaucoma
Antidepressants: SSRIs: fluoxetine, paroxetine SNRIs: duloxetine, venlafaxine, desvenlafaxine. TCA's : Amitriptyline, nortriptyline.	Narrow-angle glaucoma (occurs soon after starting of the therapy, by dilating the pupil).
Antihistamines: dimenhydrinate, diphenhydramine.	
Antipsychotics: fluphenazine, perphenazine, trifluoperazine	
Antispasmodic:fesoterodine, oxybutynin, tolterodine.	

Abbreviations: SNRI=serotonin norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

Other drugs which cause glaucoma are Sulphonamides, H2-blockers (ranitidine, cimetidine), anticholinergics (ipratropium), scopolamine, decongestants (ephedrine, naphazoline, phenylephrine).

Age-related macular degeneration is a very common eye condition in which, it causes damage to the macula (small spot near to the centre of retina). It is required for sharp and central vision, which is a leading cause of vision loss in the people of age ≥50 years. The drugs which are having chances of causing AMD includes, aspirin, some of the drugs which are used to treat abnormal heart conditions like nitroglycerin and some beta-blockers.

Cataract is the condition which involves the clouding or opacification of natural lens of the eye. Cataract formation has several etiological factors.It is induced by diabetes, myotonic dystrophy, and also by drugs such as amiodarone, corticosteroids, chlorpromazine, olanzapine, ziprasidone, and risperidone.The people with schizophrenia have the highest risk of cataract than others. Antipsychotic drugs which are used in this condition such as chlorpromazine (22%-80%), or thioridazine, are associated with ocular changes. A rare report on clozapine induced cataract in young female patient, showing about 18% of patients on antipsychotic therapy develops cataract.

A female patient of age 28years was taking clozapine25mg orally, daily at bed time since past 1 year. She presented a complaint of progressive diminution of vision in the right eye after 6 months. On examination before, found clear cornea in both eyes without any pigment deposits. Later, she was associated with corneal

endothelium pigmentation deposits and also with pigmentory retinopathy. The nature of cataract was posterior subcapsular. [5]

Other study suggests, chlorpromazine ocular toxicity results, 67% with no ocular symptoms, 20% with blurring of vision, 13.3% lacrimation,5% night blindness, 6% with yellowish pigment deposition on epithelial surface in cornea, when we consider in a population of 60 patients, in which 16 were females and 44 were males, with ages rangers from 16-50 years.[6] Bulging of eyes is not a diseasebut is a symptomatic condition for several diseases such as grave's disease, glaucoma, hemangioma and other eye related conditions. Bulging of eyes generally termed as proptosis or exophthalmos (in case of hyperthyroidism). Retinitis is an inflammation of retina of the eyes. If it is due to virus known as cytomegalo virus(CMV) retinitis, which is a herpes virus. The virus is transmitted through placental transfer, breast milk, saliva, blood transfusion, sexually transmitted fluids, bone marrow or organ transplants.

Colour blindness is a genetic condition in which reduced ability to distinguish between certain colours such as blue and yellow or red and green, affecting males more frequently than in females. Photoreceptors in retina are called rods and cones. Rods are plenty in number but incapable of perceiving colours. It is caused by neurological or metabolic disorders. But they can also be caused due to drugs such as, ethambutol, metronidazole, some of the antimalarials, digoxin, sildenafil etc.

Nyctalopia, also known as night blindness, is a condition in which difficulty or unable to see the objects in a relatively low or dim light. It is generally caused by some other eye abnormal conditions such as near-sightedness, cataracts or due to vitamin A deficiency. A study suggests, Isotretinoin (golden standard drug of choice for acne vulgaris, can cause night blindness. A 16 years old male patient with grade 3 acne vulgaris prescribed 20mg Isotretinoin, prednisolone 30mg. The patient reported back after 1 week with a complaint of reduced night vision.The dose after which the patient develops defect in his eye is 140mg.

Conjunctivitis is an inflammation of conjunctiva, which is a thin clear tissue that lies over a white part of eyes. Generally caused by bacteria or virus, associated with pain, burning, scratchiness, itchiness, red eye, watering of eyes, affecting one or both eyes. Ophthalmic medications such as antifungals, antimicrobials, antiviral, corticosteroid drops may cause hypersensitivity reactions in some patients. Preservatives such as benzalconium chloride (BAC) and its ammonium salts plays a very important role as allergens in few patients.

Table No.-4. eye related diseases and drugs which are responsible

DISEASES	DRUGS
Steven's-Johnsons Syndrome red eye	Drugs containing benzalkonium chloride
Eyelid droop	Botulinum toxin
Optic nerve disease/optic neuropathy	Amiodarone, chlorpromazine, isoniazid, ethambutol, linezolid
Corneal epithelial changes	*Amiodarone *chloroquine *chlorpromazine

	*tamoxifen (anticancer agent) *NSAID's (ibuprofen, indomethacin, naproxen) *Tinorone (antiviral) *Gentamycin, tobramycin (aminoglycoside antibiotics) * Clarithromycin (macrolide antibiotics) *cytarabin (antimetabolite) * Gold salts. Ciprofloxacin(fluoroquinolones antibiotic)
Myopia	Glibenclamide
Retinal dysfunction(retinal toxicity; retinal and vitreous)	OKT3, Phenformin + ethanol, warfarin, streptokinase, interferones.

DRUG INDUCED EAR DISEASES

An ototoxic drug is the drug that may cause damage to cochlea, auditory nerve, and vestibular system. Some drugs can cause temporary or permanent damage to the ocular system. The common drugs which cause hearing loss are, NSAID's (such as ibuprofen, naproxen, aspirin) when taken in large doses. Antibiotics such as aminoglucosides (gentamycin, neomycin, streptomycin), chloroquine, loop diuretics (furosemide, torsemide, bumetanide). The risk factors inclues, patients with kidney impairment or patient with previous history of hearing lose, genetic predisposition, advanced age. Aminoglycosides (AG's) are the well-known class of antibiotics.

All AG's causes damage to kidney (reversible) and inner ears(permanent). The damage by AG's to the inner ear which discovered by the clinical trials of streptomycin. Streptomycin damages the vestibular organ and dihydrostreptomycin causing damage to cochlea due to overdoses, accumulation or high drug retention. Gentamycin and tobramycin causes vestibulotoxic and kanamycin, amikacin (used in treatment of TB), neomycin causes cochleotoxic side effects.

Vestibolotoxicity (disequilibrium and dizziness) accounts up to 15% and cochleotoxicity (hearing loss/tinnitus)upto 2%-25% patients. [6] AG's enters inner ear through blood stream passing via middle ear. AG's targets the sensory neuroepithelium of inner ear. Presence of alkaline pH facilitates the AG's to penetrate into bacterial membrane. AG's binds to the 30s ribosomal subunits, inhibits translocation of t RNA, resulting in bacterial cell death. Some of aminoglycosides listed below:

Table No.-4. List of aminoglycosides

Amikacin	Gentamycin
Kanamycin	Tobramycin
Neomycin	Ribostamine
Streptomycin	Dehydrostreptamine

Loop diuretics which are used to treat fluid retension, causes temporary ototoxicity. It causes ringing in the ears. Chances of ototoxicity may increase, when loop diuretics are prescribed aminoglycoside antibiotics. Loop diuretics causes pathological changes in cochlea such as edematous spaces, leading to rapid decline in microphonic potential. It's invivo effects such as, it abolishes the blood circulation in the vessels which are connected to ears, leading to ischemia and anoxia.

DRUG INDUCED HEART DISEASES

The term Cardiotoxicity refers to the condition in which the heart muscles are damaged, showing the inability of the heart to pump the required amount of blood to different parts of body, which finally reduces the Quality of life. Drug induced refers to several other natural/ synthetic agents which are used in the treatment of other Diseased conditions, which finally leading to Cardiotoxicity (intentional or non-intentional). The toxic effects may be in the form of difference in the Blood pressure,Rhythm disturbances, Cellular damage, Cardiacmyopathy, Myocardial ischemia, heart failure, systemic/pulmonary hypertension, thromboembolic complication cardiac valve impairment, cardiac amyloidosis, endocarditis, shone's syndrome etc which finally leads to impairment in cardiac functions, involving different mechanisms.

Cardiotoxicity has been intensely associated with chemotherapeutic drugs including Anthracyclines (eg:doxorubicin), antimetabolites (eg: 5-FU,gemcitabine, capacitabine), vinca alkaloids(eg: Vincristin), tyrosine- kinase inhibitors and other agents. Anthracyclines, which is the most commonly used in treatment of various cancer conditions such as leukemia, breastcancer, lung carcinomas, bladder cancers, soft tissue sarcoma, solid tumors [**23]** etc, generates excess of Reactive oxygen species(ROS), causing imbalance in production of ROS/RNS, which leads to oxidative/nitrosative stress, disturbs homeostasis, by changing the blood pressure, ECG leading to various Heart complications. The cumulative dose (>550mg/m²) is considered as a risk factor for cardiotoxicity. Other clinical manifestations includes, Non-specific ST-T changes, ventricular dysfunction, pericarditis- myocarditis syndrome, finally leading to congestive heart failure. A study suggests that, out of 16 patients with cardiotoxicity, 13 patients has toxicity due to Doxorubicin. [7]

5-Fluorouracil,which is an antimetabolite, induced cardiotoxicity incidences between0-35% in the patients receiving it and mortality rate ranges between 2% to 13% .[**25**] The cardiovascular manifestations involves with 5-FU are Congestive heart failure, Angina, ventricular tachycardia, supraventricular tachycardia, Myocardial infarction, reversible cardiomyopathy and sudden death.It is administered intravenously and has a short halflife At the university of Chicago, 15 patients out of 277(5.4%) develops cardiotoxicity (MI, chest pain, sudden death) at the dose of (≥800mg/m²/day CI). [**26**]

Pre-existing cardiac abnormalities is considered as risk factors.5-FU involves in the formation of ROS, leading to oxidative stress.Capecitabine (prodrug) incidence 5.5%of 54 patients.The cardiotoxic effect of Alkylating agent (eg: Cisplatin,) is due to hydro electrolytic imbalance, experiencing Acute MI and diastolic heart failure. A Study suggesting the incidence of several toxic events with cisplatin treatment, 30% of thrombo-embolic events,38% with angina pectoris, Atrial fibrillation(12-32%), arterial hypertension(15%), and 20% with reduced Magnesium and Phosphorus levels. Other alkylating agents such as Cyclophosphamide when used in combination with anthracycline or/and trastuzumab as MDR, it leads to serious cardiotoxic complications such as heart failure(27%) with HTN, MI, thromboembolism as adverse effects. **[27]**

Patients with Imatinib (tyrosine-kinase inhibitor) treatment, develops severe Ventricular contractile dysfunction. FAERS suggests, out of 94 cases of cardiotoxicity, 58 were associated with Itraconazole which is an antifungal agent. At higher dose of Caspofungin (8.75mg/kg) and anidulafungin (25mg/kg), decrease in cardiac output resulting in various complications such as less blood supply to all other organ systems. Pooled analysis says that, current uses of 9

NSAIDs (Ketorolac, piroxicam, etoricoxib, nimesulide, indomethacin, rofecoxib, ibuprofen, diclofenac, naproxen) have the highest risk of Heart failure (20%)than in past users.[28] The incidence of causing myocardial infarction is increased by Rofecoxib when compared to all other NSAID's,[29] NSAID's inhibits the prostaglandin synthesis, which increses the peripheral systemic resistance , reduced renal perfusion,GFR,Na excretion, trigger to cause the incidence of Heart failure. The risk of heart failure increases with increasing the dose of NSAID's upto 19% admitted in hospital and risk doubles for NSAID's like diclofenac, incomethacin, etoricoxib.[28] Their exist a direct relation between Calcium and CVD when studied among older patients. It increases the incidence of CAC (Coronary artery calcium).[31]

In order to control the Viral infections, antiretroviral therapy is used,which inhibits reverse transcriptase enzyme.Eg:Zidovudin (Azothymidine,AZT),which directly inhibits ADP/ATP translocation and replication of DNA in mitochondria,their by increasing ROS production leading to cardiomyopathy. The very common and frequently observed cardiac manifestation in HIV condition are cardiacmyopathy, pulmonary hypertension, valve disease and 5328 patients with de novo diseases, in which 518 i,e., 9.8% are HIV positive . The incidence of dilated cardiomyopathy is 1.6-5% per annum and for HIV-PH, it is 0.6-5%. [32] A study says, The incidence of occurrence of hypertension in patients with HIV < 40years of age is 12-20%.But the mechanism by which ART induced hypertension is still unclear. Antiretroviral therapy induced dyslipidaemia, is characterized by increase in TC, LDL-C, VLDL-C, usually occurs within 3 months of initiation of therapy. These abnormalities are treated with NRTI, NNRTI and PI's, which worsens the existing Myocardial infarction and cardiovascular risk with the use of indinavir and ritonavir ,amplifies when lopinavir, amprenavir, and fosamprenavir (PI's) are added in multidrug regimen. Abacavir (backbone of increased CV risk), which belongs to the class nucleoside reverse transcriptase inhibitors(NRTI's), incidence the risk of myocardial infarction, by increasing LDL and total cholesterol levels in blood. [**33**] Diabetics is a major risk factor for CVD, including IHD and diabetic cardiomyopathy. The drugs like, sulfonylurea and glitazone boosts the cardiotoxicity, myocardial infarction and heart failure. Recent metaanalysis of 16 studies of 810,000 thiazolidinedione users, rosiglitazone users highly causes congestive heart failure, MI and death than in pioglitazone users. The mechanism by which they act is still unknown, but many of the mechanisms were suspected in clinical trials.

A negative inotropic property of Antiarrhythmic drugs, which is medicated by altering intracellular calcium, has an adverse effect of cardiodepressant. Patients with the history of left ventricular dysfunction, antiarrhythmic medications can induce congestive heart failure, ventricular and supraventricular arrhythmias.

Anesthetics are the medicines which causes local or general loss of sensation at a particular site. It can cause cardiac depression and hemodynamic instability. Hence, the signs and symptoms of CHF are in close relationship with anesthetics. The anesthetics such as, halogenated volatile agents(eg: Halothane and enflurane have mild inotropic effect, i.e. Cardiac depression effect. Barbiturate anesthetics (i.v) such methohexital and thiopental also causes myocardial suppression. In special populations, such as paediatrics and geriatrics, cautious dosage (higher dose is not recommended) and fluid administration may avoid undesirable effects.[**34**]

Proton pump inhibitor linked to risk for Heart failure and death in CAD patients. The risk for

Gastrointestinal complications are seen in the patients with CAD who is on chronic antiplatelet therapy, resulting in GI ulcers and haemorrhage with aspirin. The standard parameter to study the cardiac dysfunction is 'QT prolongation'. Torsade de Pointes is a very complicated condition in which sudden death occurs due to QT prolongation. Some of the drug which are responsible for this condition are as follows:

Table No.-5. List of drugs

Amiodarone	Sotalol
Bepridil	Chlorpromazine
Chloroquine	Haloperidol

DRUG INDUCED GASTROINTESTINAL DISEASES:

Some of the drugs which are responsible for causing gastro-intestine related injury or toxicity, then it is known as drug induced gastrointestinal diseases. There are many disease conditions which are caused due to wide variety of drugs. Such as, constipation, diarrhoea, nausea, vomiting, peptic ulcer disease, inflammatory bowel syndrome, cancer etc., There are also many drugs (NSAID's, ARB's, anticancer drugs, tetracycline's) which causes specific type if GI symptoms.

Overall, the adverse drug effects on GIT accounts 6.5% of hospital admissions. **(6).** The incidence rate of PUD were 0.10%-0.19% (physician diagnosed), 0.03%-0.17% (based on hospitalized data). The final study results showing reduced prevalence over the time. (**7**,).In 1998, the incidence rate was 0.12% in UK , with prevalence period of 1 year [**8**] Here are some of the drugs which causes varieties of GIT adverse effects:

Table No.-6. drugs which causes varieties of GIT adverse effects

Conditions	Drugs responsible
Dyspepsia	Taxanes, NSAID's
Acute esophagitis	Tetracyclines,bisphosphates, (>100 drugs)
Reactive gastropathy	NSAID's,
Peptic ulcer diseases/ erosion	NSAID's, corticosteroids,
Granulomatous (in stomach)	Lanthanum carbonate
Acute gastritis	Resins
Infiltrative(in case of stomach and intestine)	Clofazimine, lanthanum carbonate.
IBD	Rituximab, TNF inhibitors, NSAID's.
Colitis	Sodium phosphate, PPI's, statins, colchicine.
Ischemia (stomach, colon)	Digitalis,ergotamine, cocaine, oxygen peroxide.

Dyspepsia or indigestion is a condition in which, a group of symptoms including upper abdominal discomfort , nausea, chest pain , bloating etc. A research database suggests that, 31,232 patients using ulcer drugs, causes severe or less severe dyspepsia. Accordingly, non-steroidal anti-inflammatory drugs, calcium channel blockers, methylxanthines, corticosteroids, ACEI's. A clinical trial study results, high dose of NSAID's with any dose of indomethacin, meclofenamate increases the risk of dyspepsia by 3 times.

In the patients with non-cancerous pain, opioids are generally used. Patients usually experiences constipation, which finally may affect quality of life. Opioids are very common drugs which causes constipation with incidence rate of 40% to 86%. [**9**] It causes by increasing ring

contraction, and also by increasing the reabsorption of fluids and electrolytes. [**10**] When opioids interacts with [mu] receptors, peristaltic movements will reduce resulting in harder stool (constipation). Opioids such as methyl naltrexone, naloxegol, lubiprostone etc. Other group of drugs which induces constipation are calcium channel blockers (CCB), anticholinergics, anticonvulsants, antidepressants, NSAID's, diuretics, ß-blockers, acetaminophen, aspirin, lipid lowering agents (atorvastatin, colestyramine, colestipol), Iron (ferrous sulphate), muscle relaxant (baclofen), dopaminergics (amantadine, levodopa, bromocriptin, entacapone, tolcapone), ulcer healing agents such as proton pump inhibitors, sucralfate etc. CCB's also acts on GI smooth muscles, affecting peristalsis rate, the movement of wastes outside is diminished gradually. Generally, nifedipine, diltiazem, verapamil causes constipation in elderly patients. NSAID's such as meloxicam, aceclofenac causes hard stools and also associated with increased risk of stercoral ulcer perforation in geriatrics who have previous history of chronic constipation.Anticholinergic agents such as procyclidine, tolterodine, hyoscine, oxybutynin reduce intestinal contractility leading to constipation. [**11**]

Diarrhoea is defined as increase in the passage of loose watery stools. Chronic diarrhoea is a common problem associated with 5% of population at a given time, a prospective study says.(Lawrence R. Schiller et al., 2017). Many drugs which are used in the treatment of various infections are known to cause diarrhoea. Broad spectrum antibiotics such as ampicillin, erythromycin, neomycin etc. These increases the growth of antibiotic resistant bacteria and fungi.

Drugs which likely to cause constipation condition are: [**13**]

Table No.:7. Drugs which likely to cause constipation

Class of drugs	Examples for drugs causing constipation	Examples for drugs causing diarrhea
Alpha-blockers	Prazosin	Prazosin
ß-blockers	Oxprenolol, bisoprolol, nebivolol.	Bisoprolol, carvidilol, nebivolol.
Antacids	Aluminium and calcium salts.	Magnesium salts
Immunosuppressant	Basiliximab, mycophenolate, tacrolimus.	Ciclosporin, mycophenolate, leflunomide.
Antiepileptic	Carbamazepine, oxcarbazepine.	
Antivirals	Foscarnet	
CNS stimulant	Atomoxetine	
Antipsychotics	Phenothiazine,haloperidol, risperidol, clozapine,	
Cytotoxic drugs	Bortezomib, buserelin, doxorubicin, vincristine, vinblastine, topotecan, pentostatin, mitozantrone.	

Peptic ulcer diseases, also known as peptic ulcer or stomach ulcer is a common disease

condition worldwide. It is caused by disruption/defect of the mucous lining of stomach and duodenum, which shows imbalance between aggressive factors and defensive factors. The drugs which can causes PUD includes, NSAID's(selective cyclo-oxygenase-2 inhibitors, nitric oxide releasing) and acetyl salicylic acid (ASA), further leading to complications such as

gastroduodenal haemorrhage, perforation, obstruction, pyloric stenosis finally death.The other features of NSAID induced ulcers includes,
* More than 3mm in size
*Deep lesion
*Multiple erosion,more than 10. [**14]**

AREAS OF G.I.T. WHICH MAY BE DAMAGED BY NSAID's

Oesophagus:, ulceration, oesophagitis stricture
Stomach: ulcers, erosions
Duodenum: ulcers, erosions
Small intestine: ulcers, erosions, protein loss, strictures
Colon: exacerbation of ulcerative colitis and Crohn's disease non-specific colitis. [**15**]

NSAID's interferes with mucosal defence mechanism in stomach, inhibiting cyclooxygenase their by reducing the prostaglandin synthesis, decreases bicarbonate ions that neutralizes acid in stomach.[**16**]

Non-selective nonsteroidal anti-inflammatory (NSAID's):
Salicylate (acetylated): Aspirin
Salicylate (non-acetylated): magnesium trisalicylated, diflunisal.
Propionic acids: Ibuprofen, Naproxen, ketoprofen.
Acetic acid: Diclofenac, Indomethacin, ketorolac.
Non acidic : nabumatone
Anthranilic acid: Mefenamic acid, Meclofenamic acid
Enolic acid: Meloxicam, Piroxicam.
Selective cox-2 inhibitors:
Celecoxib, Rofecoxib, Etoricoxib, Meloxicam.

A study suggests, a survey on 1704 Rheumatoid arthritis patients were considered, as NSAID's are frequently used in the treatment such as celecoxib, etodolac, meloxicam, indomethacin, loxoprofen, diclofenac, sulindac, zaltoprofen, nabumetone, ampiroxicam, lornoxicam. 1008(59.2%) patients were currently using NSAID's. Out of which, 193 patients were found with ulcers and GI mucosal damage and 815 patients with only mucosal erosion.

595 patients (59%) were on COX-2 selective inhibitors such as celecoxib, etodolac, meloxicam. Out of which, 99 were diagnosed with ulcer or erosion with mucosal damage and 496 were only with gastric mucosal damage.[**17]** Endoscopic gastric mucosal damage in RA patients).Another study says, Upper gastrointestinal symptoms such as dyspepsia in seen in 15%-60% of NSAID users. Patients on regular NSAID use,prevalence about 15%-30%. Ibuprofen at low dose(upto 1200mg/day) and paracetamol in causing upper GI bleeding have almost same odds ratio. Naproxen, indomethacin have intermediate odds ratio and ketoprofen and azaproprazone have high odds ratio and hence it should be highly contraindicated in high risk patients. (If odds ratio is >1, then the effects of the treatment are more than those of the control treatment).

In a group of VIGOR trial study, they compared the patients who are taking naproxen 500mg BID or Rofecoxib 50mg daily in rheumatoid arthritis patients. After 6 months, they finalised as, Rofecoxib causes less severe incidence of GI events when compared to naproxen. In a CLASS study, the comparison between celecoxib 400mg B.I.D with Diclofenac 75mg b.i.d or ibuprofen 800mg b.i.d in OA and RA patients.Result showing 50% reduction in ulcer complications with celecoxib when compared to other NSAID's.

The risk of causing peptic ulcers by the use of aspirin which are frequently used in CVD or in thrombotic cerebrovascular diseases is reported as 35%. The incidence of causing gastric or duodenal ulcer with clopidogrel is 0.1% - 1%.Biphosphates which are used in the treatment of osteoporosis (prophylaxis) and in paget's disease such as

etidronate, alendronate and risedronate shows gastrointestinal side effects. Alendronate tablet do not pass through oesophagus leading to prolonged mucosal exposure of drug causing ulcers with inflammation (esophagitis). Alendronate in combination with naproxen incidence upto 38% and alendronate alone 8% .[**19**]

Potassiuum chloride retains within oesophagus resulting in haemorrhage which administered in some solid form. Hence advised to swallow the whole tablet at once with fluid. Selective serotonin reuptake inhibitors (SSRI) inhibits platelet aggregation and induces gastric acid secretion and increased GI bleeding seen in combination with NSAID's and ASA's. Aspirin and other NSAID's known to disrupt Oesophageal mucosa, leading to esophagitis and also strictures. A case control study on 1415 patients suggests, increased risk of causing peptic ulcers diseases when corticosteroid is combined with NSAID's than corticosteroids used alone.[**20**]

Retrospective study shows patients who is undergoing surgery for PUD were using cocaine and alcohol have more likely to cause duodenal perforations. The incidence rate may be 16%.(Illicit drugs).Combine use of steroids with non-steroidal anti-inflammatory drugs, increases the risk of GI bleeding. A study shows, a patient who is administering low dose of aspirin and high dose of corticosteroid, is more likely to develop upper GI bleeding than patient using arpirinalone.

NSAID's :		**Steroids :**	
Aceclofenac	100mg	Dexamethasone	4mg
Diclofenac	75mg	Betamethasone	4mg
Ibuprofen	1200mg	Prednisolone	30mg
Ketoprofen	100mg	Prednisone	30mg
Naproxen	500mg	Methylprednisolone	24mg
Mefenamic acid	1000mg	Hydrocortisone	120mg

Another case control study suggests, increased risk of getting acute pancretitis(3 times), in the patient who is on the treatment of betamethasone(within 4-14 days, adverse reaction is seen). A meta-analysis shows, PUD is rare complication of corticosteroid therapy with incidence <1.8% of patients.Here are some of the cutoff doses of NSAID's and corticosteroids, which can cause any type of GI complications, when used as long term treatment. **[22]**

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