



# Drug-Induced Liver Diseases

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Drug-induced liver diseases are gaining importance in this era of safe clinical practice and pharmacotechnological advancement. Drug-induced liver disorder is any adverse liver condition in a patient occurring as the result of treatment by a physician or herbal medicines or by any drugs self administered. Human desire to take drugs for every disease is strong.

Drug-induced liver disorders account for 2 to 5% of hospital admissions for jaundice in the U.S.A. and 10 to 20% of the cases of fulminant hepatic failure. More than 40% of these cases are over 50 years age. As similar data in our country is not available. Our hospital data shows 10% of outpatients having jaundice are due to drugs and about 20% of inpatient acute fulminant hepatic failures are due to drugs.

It has been estimated that 1 in every 5 patients is subject to some form of error during their hospital admission. 1 in 200 actually dies as a result of iatrogenic mishaps. It again emphasises the importance of safe clinical practice.

Drug-induced liver disorders mimics all forms of liver disease. Its clinical spectrum is wide. Many present as subclinical liver disease and few present as fatal fulminant hepatic failure. Nonspecific liver disorders are difficult to suspect. In fulminant drug-induced hepatic failure, recovery is late and may need liver transplantation. A single drug can cause more than one type of liver damage.

## INDIAN SCENARIO

More than 700 chemicals are used as drugs and more than 2000 formulations are used. There is widespread use of drugs

**Table 1: Presentation of drug-induced liver injury**

- \* Fatty liver
- \* Hepatitis
- \* Cholestasis
- \* Mixed liver injury
- \* Chronic hepatitis and cirrhosis
- \* Hepatic granulomas
- \* Venous-occlusive disease
- \* Budd Chiari syndrome
- \* Peliosis hepatitis
- \* Neoplasm

in cities and remote corner of villages because of aggressive sale promotions. Use of over-the-counter drugs and repeat prescription without adequate precautions are common. Many systems of medicines, Ayurvedic, Siddha, Unani and alternative system of medicine, viz., fish swallowing are common. Denial of adverse reaction by these practitioners results in non-reporting of adverse reactions. Use of allopathic drugs by unqualified persons is also common.

The coexisting factors are genetic predisposition for liver disorders, and aging population. Malnutrition may aggravate the situation. Widespread use of multiple drugs - polypharmacy complicate and precipitate liver injuries. Alcoholism and infection further predisposes the liver to injury. Hepatitis B infection and other existing chronic liver disease further increases the susceptibility to drug-induced liver disorders.

Hepatotoxicity may due to idiosyncratic reaction to drug or expected dose-related. Hepatotoxicity may present with systematic manifestation like fever, arthralgia, rashes etc. or with other organs, spleen, heart and kidney or liver alone. It can further be classified as hepatotoxicity due to drugs used for diagnostic purposes such as thorotrast or radioisotopes or due to therapeutic use.

## DRUGS PRESCRIPTION IN LIVER DISEASES

Avoiding sedative and psychotropic drugs such as diazepam, chlordiazepoxide, amitriptyline and others unless it is absolutely necessary.

Codeine sulphate and loperamide may be avoided as it may precipitate hepatic encephalopathy. Spironolactone is a safer diuretic in liver diseases. Paracetamol is relatively safer than aspirin, opiates and ergot alkaloids as analgesics, antihypertensive drugs such as diltiazem, nifedipine, verapamil and captopril may be avoided.

Most often doctors wish to know whether a particular drug has been recognised as causing liver damage. In such situation

**Table 2 : Type of Drug-Induced Reactions**

Idiosyncratic	Intrinsic
No dose dependency not reproducible in animals immunologically mediated	Dose-dependent reproducible in animals direct and indirect toxicity

**Table 3 : Common Drugs**

Predictable (dose)	Unpredictable (Idiosyncratic)
Paracetamol	Oral contraceptive
Salicylates	Amiodarone
Tetracycline	INH
Chlorpromazine	Chlorpromazine
Methotrexate	Nitrofurantoin

**Table 4 : Drugs that cause hepatitis****NSAIDs**

- Salicylates
- Paracetamol
- Diclofenac

**Antibiotics**

- Carbenicillin
- Erythromycin estolate
- Ketoconazole
- Nitrofurantoin
- Pyridium
- Sulfonamide
- Dapsone
- Ethionamide
- INH
- Rifampin

**Cardiovascular drugs**

- Acebutolol
- Labetalol
- Methyldopa
- Quinidine
- Verapamil

**Anti-epileptics**

- Felbamate
- Valproate
- Hydantoins

**Immunosuppressants**

- Methotrexate
- Cyclophosphamide
- Tacrine

**Inhalational anesthetics**

- Halothane
- Methoxyfluorane

**Miscellaneous drugs**

- Amiodarone
- Lovastatin
- Methimazole
- Propylthiouracil

British/US/Indian Pharmacopeia/Physician Desk Handbook are useful.

**Principles in using drugs in liver disease**

- Use when necessary
- Start lower dose to achieve therapeutic objective
- Consider drug toxicity - if complication occurs
- Suspect drug interaction

**Table 5 : Drugs causing chronic hepatitis and cirrhosis**

- INH
- Methotrexate
- Methyldopa
- Nitrofurantoin
- Oxyphenisatin
- Perhexiline maleate
- Trazodone

**Table 6 : Drugs causing cholestasis**

- Allopurinol
- Amitriptyline
- Azathioprine
- Captopril
- Carbamazepine
- Chlordiazepoxide
- Cyclosporine
- Diazepam
- Erythromycin
- Gold salts
- Haloperidol
- Pencillamine
- Phenytoin
- Tolbutamide

**Bland cholestasis**

- Anabolic steroids
- Androgens
- Estrogens
- Phenytoin

**Table 7 : Drugs causing mixed liver injury**

- Amitriptyline
- Amoxicillin clavulanic acid
- Ampicillin
- Captopril
- Carbamazepine
- Cimetidine
- Cotrimoxazole
- Flutamide
- Ibuprofen
- Naproxen
- Nitrofurantoin
- Phenylbutazone
- Quinidine
- Ranitidine
- Sulfonamides
- Sulindac

- Doubt, stop and consult literature.

**Diagnosis of Drug-induced liver injury**

Clinical situation: Patient on drugs and develop some adverse liver injury subsequently. It is exclusion diagnosis - excluding other causes. Consider the possibility of a drug for hepatotoxicity. Tabulate drugs taken by patient both prescribed by doctors and self-administered.

- Relate drugs to onset of illness

**Table 8 : Drugs causing steatosis**


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- Amiodarone
- Aspirin
- Ketoprofen
- Tetracycline
- Valproic acid
Macrovesicular steatosis
- Cisplatin
- Corticosteroids
- Methotrexate
- Paracetamol
- Tamoxifen
- Zidovudine

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**Table 9 : Drugs associated with hepatic granulomas**


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- Allopurinol	- Nitrofurantoin
- Para-amino salicylic acid	- Oral contraceptive pills
- Carbamazepine	- Penicillin
- Cephalexin	- Phenylbutazone
- Clofibrate	- Phenytoin
- Diazepam	- Procainamide
- Diltiazem	- Procarbazine
- Erythromycin estolate	- Quinidine
- Gold salt	- Silicone
- Halothane	- Starch
- Hydralazine	- Sulfasalazine
- INH	- Sulfonamide
- Methyl dopa	- Sulfonylurea derivatives
- Metolazone	- Talc

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**Table 10 : Drugs causing veno-occlusive disease**


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- Azathioprine
- Carmustine
- Doxorubicin
- 6-mercaptopurine
- Pyxrolidzine alkaloids (medicinal bush tea)
- 6-thioguanine
- Vincristine

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- Look for preexisting liver disease
  - Clinical examination
  - Previous laboratory investigation.
  - Consider alternate causes
    - Viral hepatitis - Serological markers
    - Biliary disease - Ultrasound examination.
  - Observe the effects of stopping drugs
  - Liver biopsy - suspected pre-existing liver disease
    - Failure to improve
    - Challenge test with drugs - never (hardly ever)
7. Liver is the major site of drug metabolism. Both phase I reaction - Oxidation occurs in the smooth endoplasmic Reticulum. Phase II reactions - conjugation - glucourination takes place in mitochondria of hepatocyte. First phase metabolism, volume of distribution of drugs, half-life, protein binding and clearance of drugs effect the liver.

**Table 11 : Drugs associated with Budd-Chiari syndrome**


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- Arsenical derivatives
- Cyclophosphamide
- Dacarbazine
- Oral contraceptive pills
- Vincristine

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**Table 12 : Drugs associated with peliosis hepatitis**


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- Anabolic steroids
- Androgens
- Arsenical derivatives
- Corticosteroids
- Medroxy progesterone
- Oral contraceptive pills (?)
- Tamoxifen
- 6-Thioguanine

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**Table 13 : Drugs associated with neoplasm**


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- Anabolic steroids
- Androgens
- Oral contraceptive pills
Hepatocellular carcinoma
- Anabolic steroids
- Methotrexate (?)
- Oral contraceptive pills (?)
- Oral hypoglycemic agents (?)
- Thorium-dioxide
Angiosarcoma
- Anabolic steroids
- Androgens
- Arsenical derivatives
- Oral contraceptive pills
Cholangiocarcinoma
- Anabolic steroids
- Androgens
- Methyl dopa
- Oral contraceptive pills

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**Prevention of Hepatotoxicity - Surveillance**

Needs continuous monitoring, Liver function tests are of limited value. Transient rise of transaminases are common in 5-20% of cases. Surveillance is important for new drugs or known hepatotoxic drugs particularly within 12 weeks of starting drugs. Identifying hepatotoxic in surveillance is limited as some drugs like methotrexate and amiodarone produces extensive liver damage before raising the enzymes.

Judicious use of tested safe, well-known effective familiar therapeutic drugs with a strong dose of caution is necessary for safe clinical practice.

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