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**Review Article**

# Review on drugs inducing hepatotoxicity

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**ABSTRACT**

Drug-induced liver injury is a frequent cause of hepatic dysfunction. Chemicals that cause liver injury are called Hepatotoxins. For establishing hepatotoxicity of a particular drug, exclusion of other plausible causes is needed prior. The pattern of liver test abnormality, duration of latency to symptomatic presentation, the presence or absence of immune-mediated hypersensitivity and the response to drug withdrawal are needed for establishing hepatotoxicity of a drug. The liver plays an astonishing array of vital functions in the maintenance and regulation of body homeostasis. The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamin. Liver is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. Thus, maintenance of healthy liver is a crucial factor for the overall health and wellbeing. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure liver. Other chemical agents, such as those used in laboratories and industries, natural chemicals and herbal remedies can also induce hepatotoxicity. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures.

**Keywords**: Liver, hepatotoxicity, hepatotoxins, drugs

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## INTRODUCTION

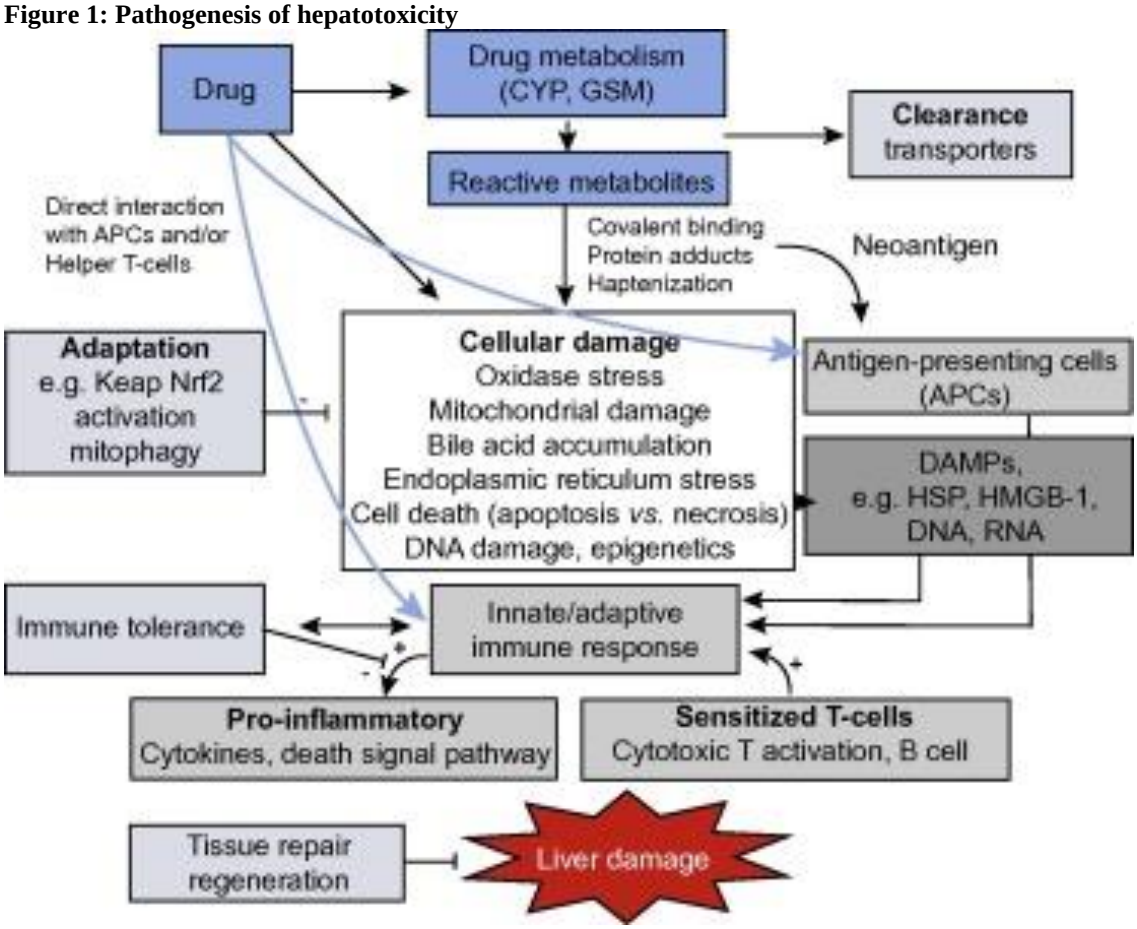
Hepatotoxicity is the primary cause of drug-related deaths and the principal reason that pharmaceuticals are withdrawn from the market. Despite improvements in toxicological studies and in safety analyses in clinical trial protocols, the frequency of drug-induced liver injury has not decreased over the past 10 years. All liver cells can be affected by drugs. The types of lesions vary according to the mechanism of drug action, the role of the parent drug or one of its metabolites, the route of drug administration, the drug dosage, and the susceptibility of the patient. Consequently, adverse reactions to drugs affecting the liver can reproduce the entire spectrum of noniatrogenic liver diseases. More than 1100 classic drugs are known to provoke hepatotoxic reactions. Furthermore, some drug-associated excipients, herbal medicines, and recreational or illegal compounds (such as amphetamines and cocaine) are also hepatotoxic. Drug-induced morbidity and mortality of are of concern to physicians, health authorities, and pharmaceutical companies, and it is important to understand and manage the most critical aspects of potential hepatotoxicity.

**Table 1: CLINICAL FEATURES OF DRUG-INDUCED LIVER DISEASE**

| DISEASE | DRUGS CAUSING THE FEATURE |
|---|---|
| Acute Hepatitis | Acetaminophen, Bromfenac, Isoniazid, nevirapine, Ritonavir, Tioglitazone |
| Chronic Hepatitis | Diclofenac, Methydopa, Nitrofurantoin, |
| Acute Cholestasis | ACE Inhibitors, Chlorpromazine, Amoxicillin/Clavulanic Acid |
| Atypical Hepatitis | Phenytoin, Sulfonamides |
| Non-alcoholic Steatohepatitis | Amiodarone, Tamoxifen |
| Cirrhosis | Methotrexate |
| Venocclusive Disease | Busulfan, Cyclophosphamide |

## PATHOGENESIS

**Figure 1: Pathogenesis of hepatotoxicity**



## HEPATOTOXIC DRUGS

**Anti-Tubercular Drugs:** The first line anti-tubercular drugs namely, Rifampicin, Isoniazid and Pyrazinamide are potentially hepatotoxic drugs. These drugs are metabolized by the liver. No hepatotoxicity has been described for Ethambutol or Streptomycin. Adverse effects of Anti tubercular therapy are sometimes potentiated by multiple drug regimens. Thus, though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is enhanced. Based on hepatotoxicity diagnosis criteria and population under study, incidence of anti-TB related hepatotoxicity is reported from 2% to 28%.

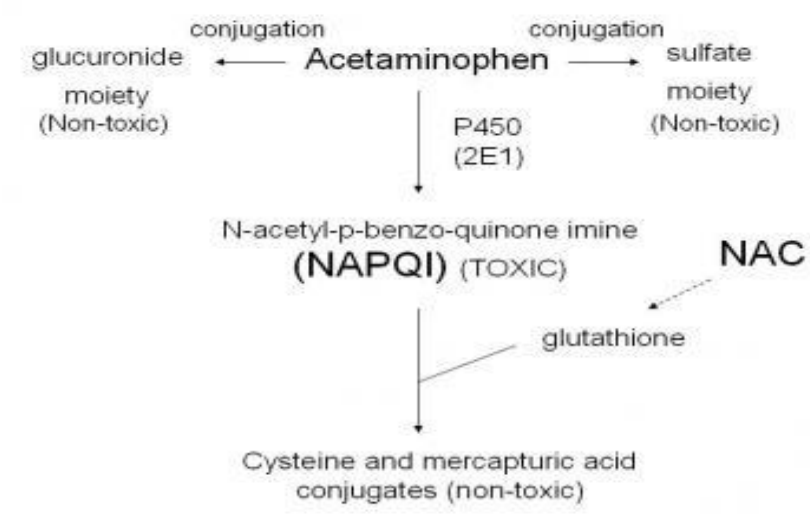
**Isoniazid**

Isoniazid (INH) remains a mainstay for the treatment of tuberculosis despite the fact that it can cause liver failure. Previous mechanistic hypotheses have classified this type of drug-induced liver injury (DILI) as 'metabolic idiosyncrasy' which was thought not to involve an immune response and was mainly due to the bioactivation of the acetyl hydrazine metabolite. It is a common complication of Antituberculosis therapy that ranges in severity from asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P450 leading to hepatotoxicity. Human genetic studies have shown that cytochrome P4502E1 (CYP2E1) is involved in Anti tubercular drug hepatotoxicity. The CYP2E1 c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins.CYP1A2 is suggested to be involved in hydrazine detoxification. Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes. [1]

## NON STEROIDAL ANTIINFLAMMATORY DRUGS

**Acetaminophen**

Acetaminophen related hepatotoxicity is now the most common cause of the potentially devastating clinical syndrome of acute liver failure in many western countries. Most such instances are the consequence of ingestion of large paracetamol overdoses.




Cases of severe hepatotoxicity following modest overdoses of up to 10 g daily, or even after ingestion of recommended doses , have also been reported in patients taking paracetamol for therapeutic purposes, mostly over several days to weeks, in association with concomitant chronic alcohol exposure or use of other cytochrome P450 enzyme-inducing drugs. In patients who develop liver damage following moderate paracetamol overdose up to 10 g daily, recent fasting and nutritional impairment have been identified as key precipitants.[2]

**Diclofenac**

Diclofenac belongs to non-steroidal anti-inflammatory drug (NSAID) family. It is a phenylacetic acid derivative which is well-known for its analgesic and anti-inflammatory properties. Also, its antipyretic and anti-bacterial effects have been reported. Despite the therapeutic actions of DF, it has notable adverse effects. Diclofenac hepatotoxicity is an archetype of idiosyncratic Drug induced liver injury.About 15% of those patients regularly taking diclofenac develop elevated levels of liver enzymes, and a threefold rise in transaminase levels has been reported in 5%.Diclofenac is associated with a predominantly hepatocellular pattern of liver injury, but a cholestatic pattern of liver injury and cases resembling autoimmune hepatitis have also been described. In addition to 4′-hydroxylation by cytochrome P450 2C9, diclofenac undergoes

glucuronidation by UDP-glucuronosyltransferase-2B7 to form an unstable acyl glucuronide.Both diclofenac acyl glucuronide and benzoquinone imines derived from 5-hydroxydiclofenac modify proteins covalently; hence, decreased as well as increased activity of CYP2C8 potentially increase the risk of hepatotoxicity.[3,4]

## ANTI-RETROVIRAL DRUGS

Liver toxicity is more frequent among subjects with chronic hepatitis C and/or B. The incidence of drug induced liver toxicity is not well known for most anti retrovirals. Liver toxicity, especially severe toxicity, is clearly more frequent in HCV (Hepatitis C) and/or HBV (Hepatitis B) coinfected individuals treated with HAART (Highly active antiretroviral therapy usually combination of two or three drugs).

**Protease inhibitors:**

Examples: Ritonavir, Indinavir, Saquinavir, Nelfinavir

Hepatotoxicity became more evident after the introduction of Anti-retrovirals of high activity, which initially included invariably a protease inhibitor. However none of the studies has been able to prove the higher potential for liver toxicity of this particular family of drugs.The antiretroviral protease inhibitors act by binding to the catalytic site of the HIV protease, thereby preventing the cleavage of viral polyprotein precursors into mature, functional proteins that are necessary for viral replication. Most of these agents were developed by rational drug design based upon chemical structures that would interact with the catalytic site of the HIV protease, based upon x-ray crystallographic studies defining the three-dimensional molecular structure of the protease. For these reasons, the protease inhibitors are heterogeneous molecules with little structural similarity, most of which are peptide-like and resemble the short peptide that is cleaved by the viral protease (usually the N terminal side of the middle proline residue is phenylalanine-proline-proline).

Among the Protease inhibitors, fulldose ritonavir has been found to be hepatotoxic, although the study results have not been confirmed by others. In certain cases, RTV has caused fatal acute hepatitis. Nelfinavir was found to be less hepatotoxic than the other Protease Inhibitoranalysed. [5]

**Nucleoside analogues reverse transcriptase inhibitors**

NRTI Examples: Lamivudine (3TC), Tenofovir, Zidovudine, Didanosine, Stavudine, Abacavir (ABC) and Tenofovir (TDF).

The majority of the NRTI can induce mitochondrial damage, and, therefore, have a potential for the development of liver injury. Cases of hepatic failure have been reported in patients taking zidovudine, but didanosine and stavudine have been most often involved in severe hepatotoxicity.Within the non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz can be considered a safer drug for the liver than nevirapine. In fact, the frequency of severe increased liver enzymes in patients on efavirenz ranges from 1 to 8%, whereas in patients treated with nevirapine, it ranges from 4 to 18%. Likewise, nevirapine is more commonly associated than efavirenz with early acute hepatitis, which is produced by a hypersensitivity mechanism and has a defined risk profile that often makes it avoidable. Despite the fact that most cases of NNRTI-induced liver toxicity are asymptomatic, the rates of symptomatic events in patients treated with nevirapine are greater than in subjects on efavirenz. In any case, it is unusual for an NNRTI to be suspended due to liver toxicity. Abacavir (ABC) and tenofovir (TDF), with low potential for mitochondrial damage, seem to have a safer profile regarding the liver.[6]

**Non-nucleoside analogues reverse transcriptase inhibitors**

Examples: Nevirapine, Emtricitabine, Efavirenz.

The risk of liver toxicity associated with the Non nucleoside analogues reverse transcriptase inhibitors (NNRTI) is variable and involves several aspects and mechanisms. It is interesting that one of the studies did not find cross hepatotoxicity between NVP and EFZ. In the same study, the morbidity and mortality derived from liver toxicity among patients taking NVP or EFZ was similar. Moreover, in a study assessing NVP hepatotoxicity, transaminases level was found to be decreased in many patients who continued taking the same treatment. [8,9]

## ANAESTHETIC AGENTS

These are the agents who cause reversible loss of pain and sensation. These are of two types, local anaesthetics and general anaesthetics. These agents cause hepatocellular damage and interfere with bilirubin metabolism and cause cholestasis.

**Nitrous oxide**

Nitrous oxide (NO) was found to have a facilitatory role in virtually all cases of unexplained hepatitis. Possible role could involve increased risk of hypoxia, and inhibition of methionine synthetase. Harmful effects of enhanced NO production in the liver include inhibition of mitochondrial respiratory chain enzymes and gluconeogenesis. [11]

**Halothane**

Halothane was introduced into use as an anaesthetic in 1956, and replaced ether as the

anaesthetic of choice. Two types of halothane-mediated hepatotoxicity have been defined: The first type, type I, is a mild, self-limited postoperative hepatotoxicity, with a mild form of hepatocellular injury that can be observed in about 20% of halothane-treated patients. The mild hepatic injury is assumed to result from the direct action of halothane on the liver cells. Two clinically detectable factors appear to contribute to the mild form of hepatic injury. [14] The first is a transient elevation of liver enzymes and the second is alteration of cellular integrity, which can be detected by electron microscopy. Lesions result from intracellular degradation of halothane via its anaerobic and aerobic pathways in combination with local hypoxia caused by an alteration of the hepatic oxygen demand and supply relationship. The second type of halothane-mediated hepatotoxicity is type II halothane hepatitis. [15]

**ANTI-RHEUMATIC DRUGS**

Anti-rheumatic agents are among commonly used drugs associated with adverse hepatic reactions. Sulfasalazine and azathioprine are among the most important causes of acute hepatotoxicity. A population-based case–control study that included 1.64 million subjects found sulfasalazine and azathioprine to be among the most hepatotoxic drugs of any class, both associated with an incidence of liver injury of about 1 per 1,000 users.

**Sulfasalazine**

The DMARD sulfasalazine is commonly used to treat RA and psoriatic arthritis. The estimated incidence of serious hepatotoxicity was higher in a cohort of patients with inflammatory arthritis. The majority of cases occur within the first month of starting sulfasalazine therapy, and these can present either as a hepatocellular or cholestatic pattern of liver injury. About 25% of patients are jaundiced and a proportion of these rapidly develop hepatic failure. [16]

**TNF inhibitors**

Elevated levels of transaminases have been described following treatment with the three most extensively studied TNF inhibitors- adalimumab, etanercept and infliximab. The overall frequency of these events depends upon the threshold used to define hepatotoxicity. ALT enzyme level may found to be elevated in the study conducted. Hepatic sinusoids are involved in the clearance of immune complexes via Fc receptor-mediated interactions that in turn could activate Kupffer cells to release reactive oxygen species or lead to local hepatocyte damage. Variability in the reported frequency of hepatotoxicity with antiTNF agents could be related to the fact that monoclonal antibodies form immune complexes more readily than soluble receptors. [17]

**ANTI-PSYCHOTIC DRUGS**

Hepatotoxicity of psychotropic drugs occurs in variable but small proportion of users and therefore can be considered unpredictable or idiosyncratic. Asymptomatic mild transient and reversible elevations of liver enzymes occur infrequently with both first and second generation antipsychotic drugs. These abnormalities occur during the first three months of treatment.[18]

**Chlorpromazine (CPZ)**

Chlorpromazine has been the most extensively studied. The clinical features appear to be accounted for by a mix of hypersensitivity reaction and metabolite toxicity. Chlorpromazine was recognized to produce jaundice. Chlorpromazine is the most extensive studied neuroleptic and the type of hepatic injury that CPZ produce is the prototype of the hepatocellular cholestasis. The mechanism of phenothiazines-induced cholestatic disease remains uncertain. [19]

**Haloperidol**

Haloperidol, while structurally similar to phenothiazines, is a very rare cause of overt liver disease. The features resemble phenothiazines-induced cholestatic injury. Chlorpromazine and Haloperidol have an identical heptanoic acid side chain and rarely, have been associated with microvesicular steatosis. The side chain is metabolized by oxidation leading to inhibition of medium- and short-chain fatty acid β-oxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individuals. [20]

**ANTI-EPILEPTIC DRUGS (AED)**

Liver injury associated with antiepileptic drugs is well recognized. The frequency of the most common AED is rare but the consequences can be very serious leading to death or liver transplantation due to acute liver failure induced by these drugs. The mechanisms behind hepatotoxicity induced by AED are not clear. [21]

**Carbamazepine (CBZ)**

Carbamazepine is a widely used antiepileptic drug, and regarded as the choice of drug for the grandmal epilepsies. It leads to increase in gamma glutamyltransferase and lesser extent in alkaline phosphatase, due to its enzyme-inducing properties. CBZ may lead to cholestatic and hepatocellular injury, even granuloma formation in the liver. [22]

**Phenytoin**

Phenytoin hepatotoxicity is a serious idiosyncratic reaction that occurs in less than one percent of patients. The phenytoin hepatotoxicity can elevate the level of aminotransferases, lactic dehydrogenase, alkaline phosphatase, bilirubin, and prothrombin time in serum. Although the exact mechanism of phenytoin hepatotoxicity is unknown; the majority of literature supports a hypersensitivity mechanism. [23]

## ANTI-HYPERLIPIDEMIC DRUGS

The proposed mechanisms of hepatotoxicity are varied depending on the drug or drug class, and include effects on the cytochrome P450 system, impairment of bile acid transport proteins, immune-mediated inflammatory response to the medication or its metabolites, immune-mediated apoptosis by tumour necrosis factor, and oxidative stress due to intracellular damage. The antihyperlipidemic drug with the highest potential for hepatic injury is the sustained-release formulation of niacin. HMG CoA reductase inhibitors, otherwise known as statins, very rarely cause clinically significant liver injury, although asymptomatic elevation in amino transferases is common.

**Statins**

Initial studies of statins performed on animals revealed that very high doses of statins may cause hepatotoxicity, but typical therapeutic doses of the drug were not associated with significant liver injury. High doses of lovastatin caused significant hepatocellular necrosis in rabbits. This pattern of injury was also seen in a guinea pig model exposed to high doses of simvastatin. However, hepatocellular necrosis from statins is exceptionally rare in humans.[24]

**Atorvastatin**

Atorvastatin-related hepatotoxicity has been associated with a mixed pattern of liver injury typically occurring several months after the initiation of the medication. There has also been a recent case report of underlying autoimmune hepatitis apparently revealed by atorvastatin. After broad experience with this medication, significantly increased transaminases levels greater than 3 times the upper limit of normal were only seen in 0.7% of cases.[25]

## ANTI-HYPERTENSIVE DRUGS

**Methyldopa**

Methyldopa is used in the treatment of hypertension. Both minor and severe forms of liver damage have been reported in patients receiving methyldopa. The former consists of asymptomatic, and often transient, rises of serum transaminases and according to various reports is found in two to 10 % of patients receiving the drug.Drug induced liver injury due to methyldopa was identified shortly after its introduction into medical use in the 1960's. Chronic use of methyldopa is associated with mild and transient elevations in serum aminotransferase levels in 5% to 35% of patients, these elevations often resolving despite continuation of the medication. In contrast, clinically apparent or significant liver injury from methyldopa is relatively uncommon, although several hundred cases have been reported. Two patterns of hepatotoxicity have been described: an acute hepatitis that appears within weeks to months of starting treatment, and a chronic hepatitis that arises months to years after initiation of methyldopa therapy. The liver damage, which may take the form of acute hepatitis, chronic active hepatitis or cholestasis occurs more commonly in women and there is not the same close temporal relationship between the time of onset of overt clinical hepatic injury, which in 50% of cases occurs after four weeks.[27]

## ANTI-DEPRESSANTS

Most tricyclic antidepressants are potentially hepatotoxic. Although other tricyclics (including amitriptyline, desipramine rarely cause liver disease the reported cross-reactivity should preclude their use when sensitivity to one has been suspected.

**Amineptine**

Amineptine-induced liver disease is mainly cholestatic, although moderate necrosis may be seen. The compound has a heptanoic acid side chain. The side chain is metabolized by βoxidation, leading to inhibition of medium- and short-chain fatty acid beta-oxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individuals.

**MAO inhibitors**

MAO inhibitors, which derive from hydrazine, are all potential hepatotoxins. Hydrazines can be metabolized by P450 to toxic intermediates. Their metabolism and mechanism resemble that of isoniazid, also a hydrazine. One substituted hydrazine MAO inhibitor remains available, namely phenelzine; there have been case reports of hepatitis. [30]

## CONCLUSION

The list of hepatotoxic drugs is huge and a complete coverage is difficult. To sum up thus there are a large category of drugs used for different therapeutic indications which are toxic to the liver and thus should be cautiously administered; particularly when given at high doses

or used for chronic or long term administration. Hepatotoxicity is well recognized with hormonal agents, their corresponding antagonists, Anabolic Androgenic Steroid (AAS), Anti-thyroid drugs etc. The spectrum of drug induced liver diseases ranges from acute hepatitis, cholestasis, and hepatic vascular toxicity through to benign and malignant liver tumors. Considering the importance of drug-induced hepatotoxicity as a major cause of liver damage, this review throws light on various drugs which induce hepatotoxicity, with their mechanism of liver damage and clinical scenario.

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