
# Pathogenetic Mechanisms of Liver Damage in Toxic Hepatitis


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ABSTRACT

The aim of this study is to prepare an updated list of drugs that cause hepatotoxicity and to identify drugs that, according to scientific data, are most likely to cause hepatotoxicity. Some aspects of hepatotoxic drugs are like manifestation of hepatotoxicity, type of injury, mechanisms of hepatotoxicity, risk factors and clinical manifestations. Three categories were established to assess the likelihood of hepatotoxicity and the type of injury: certain, probable, and possible. The list is made up of 181 drugs and 17 combination dosage forms or therapeutic regimens that can cause hepatotoxicity. Of these, methotrexate, minocycline, vancomycin, everolimus, isoniazid, and tamoxifen are categorized as certain probabilities.In conclusion, over 180 hepatotoxic drugs were identified, of which six were categorized as certain probabilities and most were categorized as possibilities. Summarizing the information shows that various categories of drugs can cause toxic effects on the liver.



**Keywords:** hepatotoxicity; hepatitis; liver damage; risk factors; neoplasia.


**Relevance.** Chronic hepatitis is a polyethiological disease, the main etiological factors of which include hepatitis viruses, parasitic diseases, toxic factors, alcohol, cholelithiasis and etc. [52]. One of the most common causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [39]. Autoimmune hepatitis is a complex disease, wich is characterized by the presence of hypergammaglobulinemia and autoantibodies against hepatocytes [40].

Hepatotoxicity is damage caused by exposure to a drug or non-pharmacological agent. Risk factors include: individual intolerance, age, gender, alcohol use, smoking, concomitant use of other drugs, liver disease, genetic and environmental. [1-3]. Although most lipophilic drugs can cause hepatotoxicity, [4] antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are the pharmacological groups that are the most common causes [5-9]. Intravenous drugs include antibiotics and neoplasia drugs most associated with liver toxicity. [10].

Hepatotoxicity can be divided into intrinsic and idiosyncratic reactions. The former are predictable, dose-dependent, and reproducible, but have limited information about their frequency of occurrence. Idiosyncratic reactions are either immune or metabolic and are unpredictable, dose-independent and non-reproducible, but they affect only a small proportion of patients (between 1/1000 and 1/100,000 of patients studied). Internal hepatotoxicity is less common than idiosyncratic hepatotoxicity [12, 18-20]. Liver histology is ideal for identifying patterns of liver toxicity, but in clinical practice most hepatotoxic lesions are classified according to biochemical tests [21]. According

to the international consensus of the Council of International Organizations for Medical Sciences (CIOMS), with liver damage, liver enzymes are present at twice the upper limit of normal (ULN). On the other hand, the types of damage are classified:

• Hepatocellular damage is defined as an isolated increase in alanine aminotransferase (ALT) more than twofold or an ALT/alkaline phosphatase ratio greater than five. Hee's law defines this type of injury as an ALT value greater than three times the TPN. [24, 25]

• Cholestatic damage is defined as a single increase in alkaline phosphatase greater than twice the ULN or a ratio less than two.

• Mixed damage is defined as ALT and alkaline phosphatase levels greater than twice the upper limit of normal and a ratio greater than two but less than five.

Hepatotoxicity is associated with mitochondrial dysfunction, inhibition of cellular respiration, or altered fatty acid β-oxidation [6, 27]. This leads to apoptosis, necrosis, autophagy and, consequently, cell death [28, 29].

The main clinical and pathological manifestations of hepatotoxicity and histological data:

a. Acute hepatitis (characterized by inflammation of the parenchyma, necrosis in Kupffer cells and sinusoids).

b. Chronic hepatitis (fibrosis)

c. Fulminant hepatitis (necrosis and inflammation)

d. Cholestatic hepatitis (inflammation and damage to the liver)

e. Cholestasis (bile plugs in zone 3)

f. Vanishing bile duct syndrome (bile duct injury, cholestasis, and inflammation)

g. Granulomatous hepatitis (granulomas in the portal tracts or parenchyma)

h. Macrovesicular steatosis (lipid droplets in the cytoplasm of the hepatocyte)

i. Microvesicular steatosis (tiny droplets of lipids in the cytoplasm of the hepatocyte)

j. Steatohepatitis (steatosis, lobular inflammation, accumulation of hepatocytes and pericellular fibrosis) [12, 29-31].

These manifestations are accompanied by nonspecific signs and symptoms such as fever, fatigue, nausea, pain, jaundice, dark urine, pruritus, ascites, encephalopathy, and elevated transaminases [16, 32, 33].

Although about 1100 drugs, excluding substances found in natural products, have been associated with hepatotoxicity [19], identifying this adverse event is a difficult task.

Therefore, a thorough investigation is required to identify any substance and rule out other causes of liver disease (3, 8, 34). In addition, liver biopsy is fundamental for determining hepatotoxicity [35]. The chronological relationship between exposure to the suspected agent and the hepatotoxic reaction is key.

To establish the likelihood that a drug is associated with hepatotoxicity, clinical scores such as the Roussel-Uklaf causality method (RUCAM) and the Maria &Victorino (M&V) clinical score have been developed. It is believed that the content of the RUCAM scale and the validity of the criterion make it the most appropriate, and that it generates results consistent with medical judgment and expert judgment on hepatotoxicity. However, due to its high application cost, its usefulness in clinical practice is limited [36, 41, 42]. In the absence of specific pharmacotherapy, treatment of hepatotoxicity is based on withdrawal of the suspected drug, treatment of symptoms, and subsequent laboratory preliminary tests [43]. However, the use of N-acetyl cysteine as an antidote for paracetamol toxicity and hepatotoxicity due to phenytoin and carbamazepine, as well as the use of drugs for the treatment of valproic acid poisoning [44].

An updated list of hepatotoxic drugs and related factors may help optimize detection and prevent this adverse event. Therefore, the objectives of this review were to provide an updated list of drugs associated with hepatotoxicity and to identify, according to scientific evidence, the drugs most likely to cause hepatotoxicity.

PubMed/Medline searches were performed using the MeSH terms "liver disease" (drug exposure, injury, pathology) and "drug-induced liver injury". The search was filtered by published articles with keywords in

the title or abstract up to December 2020 in English, Spanish and French and for which full text was available.

The articles were classified as case reports, reviews, systematic reviews, clinical trials, clinical trials, controlled trials, randomized clinical trials, clinical trials, meta-analyses. Articles with evidence of hepatotoxicity due to medication alone and those considered relevant to the subject were included.

Mechanisms of hepatotoxicity, risk factors, clinical manifestations, management, outcome, measurements, liver enzymes and drug dosages were also recorded.

Means and standard deviations were calculated for numerical values. Theoretical data such as liver enzyme values (aspartate, aminotransferase [AST], ALT, FA, and total bilirubin [TB]) and doses of drugs administered.

The search identified 610 articles, of which 402 met the inclusion criteria and were selected, while 208 did not meet the inclusion criteria and were excluded. Forty-six other articles deemed relevant to the review were included.

A list of 181 drugs and 17 combined pharmacological dosage forms or therapeutic regimens that can cause hepatotoxicity. Six of these drugs (methotrexate, minocycline, vancomycin, everolimus, isoniazid, and tamoxifen) and one regimen (isoniazid, rifampicin plus pyrazinamide) were classified as certain drugs and five combination dosage forms or regimens were classified as probable, and 119 drugs and 11 combination dosage forms were classified as possible.

The type of lesion caused by each drug has been identified, and hepatocellular damage is more common than cholestatic or mixed lesion. Information was found for each drug with a certain probability, which was tabulated, type of hepatotoxicity, type of lesion, appearance, mechanism of hepatotoxicity, risk factors, clinical manifestations and results.

More cases of amiodarone have been reported and have been associated with increased hepatic enzyme synthesis in 15–55% of patients [50].

Antihypertensive agents such as enalapril increase liver enzymes and produce jaundice and structural liver biopsy evidence that has resulted in transplantation and death [53].

For methyldopa (probable), nine cases have been reported. idiosyncratic liver toxicity [17]. They had a pattern of hepatocellular injury, especially in women, showing jaundice, anorexia, and nausea. In addition, liver biopsy revealed necrosis and inflammatory infiltrates [54, 55].

Hepatocellular lesions accompanied by elevated liver enzymes, jaundice, fever, and asthenia have been associated with atorvastatin and ezetimibe [56, 57].

Propylthiouracil caused the death of one patient, affecting women and girls, causing symptoms such as jaundice, pruritus, and weight loss; necrosis, fibrosis, inflammatory infiltrate and was found on liver biopsy.

Four cases of elevated liver enzymes, weakness and jaundice were identified in patients taking methylprednisolone. Symptoms improved after drug withdrawal [59]. Among antibiotics, there have been idiosyncratic reactions identified in combination with vancomycin [60], especially reverse transcriptase inhibitors, nucleoside analogs and protease inhibitors, can cause dose-dependent hepatotoxicities. Efavirenz and nevirapine have been reported to have elevated transaminase levels and an incidence of 1% to 14% [9]. Co-infection with hepatitis B or hepatitis C virus may increase the level of hepatotoxicity associated with antiretroviral treatment.

Chemotherapy increases life expectancy but can cause liver damage ranging from steatosis and steatohepation to cirrhosis. The likelihood of hepatotoxicity for tamoxifen, everolimus, and methotrexate is certain.

Medications such as flutamide, etoposide, imatinib, ipilimumab, oxaliplatin, temozolomide, thioguanine, glatiramer, azathioprine, and infliximab have been classified as likely causes of hepatotoxicity.

Women affected by minocycline aged 16 to 57 who were diagnosed with autoimmune hepatitis. Rifampicin has caused hepatocellular lesions and women are particularly affected

[62, 63] The following antibiotics have been classified as likely causes of hepatotoxicity: nitrofurantoin (incidence 12% of cases, idiosyncrasy), [64, 65], flucoxacillin (11 cases, idiosyncrasy), [66] telithromycin (hepatocellular lesions with elevated transaminase levels and fever), [67] ciprofloxacin and trovafloxacin (withdrawal from the market).

Liver damage associated with the antifungal agents itraconazole, fluconazole, and ketoconazole improved with the drug suspension. [68].

NSAIDs have been identified as an important group that can cause liver damage, mostly idiosyncratic, in cases of abuse or overdose. Identified risk factors included age, female gender, chronic alcohol use, consumable drugs, underlying medical conditions, obesity, type 2 diabetes, and stroke. Pathogens include diclofenac, lumiracoxib, and nimesulide. Acetaminophen is widely recognized as an intrinsic hepatotoxic agent due to metabolites that cause hepatic necrosis.

When taking N-acetylcysteine and prednisolone, the condition improved in some patients.

Halothane was the general anesthetic most likely to cause liver toxicity. Genetic predisposition, repeated doses, obesity is a combination of isoniazid, rifampicin and pyrazinamide (certain probability). Hepatotoxicity manifests with elevated liver enzymes, abdominal pain, jaundice, asthenia, nausea, vomiting, and necrosis and is confirmed by liver biopsy. In the case of combined pharmaceutical dosage forms of antibiotics, such as trimethoprim/sulfamethoxazole and amoxicillin/clavulanic acid, cases of hepatotoxicity were identified as idiosyncratic and classified as probabilistic [62]. Hepatotoxicity was observed mainly in men and caused jaundice and itching. In some cases caused by amoxicillin/clavulanic acid, the result was a liver transplant.

The ritonavir antiretroviral regimen, indinavir, darunavir and fosamprenavir have been associated with hepatocellular injury and necrosis. Case reports of the anticancer drugs 6-thioguanine, daunomycin, and cytosine arabinose used as part of a therapeutic regimen for childhood myelogenous leukemia have shown hepatomegaly, cirrhosis, and veno-occlusive disease.

Risk factors were age and advanced age. Women are more likely to suffer from liver damage, including hepatocellular damage, elevated liver enzymes, necrosis, fever, jaundice, and fatigue.

Among anticonvulsants, valproic acid was the most important, the number of cases of hepatotoxicity (hepatocellular type), which is manifested by elevated transaminases, jaundice and anorexia. In addition, microvesicular and macrovesicular steatosis, necrosis, and inflammatory infiltrates were found on liver biopsy. This medicine can cause liver damage in people under 30 years of age.

Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [41]. Timely diagnosis of chronic hepatitis and liver cirrhosis and appropriate will reduce the risk of many complications [42].

The identified cases of carbamazepine were mainly of mixed type with the formation of granulomas.

**Conclusions**. We have identified over 180 drugs associated with hepatitis toxicity. Of these, six have definite probabilities, while most of the rest have possible probabilities. Notably, more than 50% of drugs found are associated with idiosyncratic hepatotoxicity, and female gender is the main risk factor. The age range of people suffering from the disease is wide.

In addition, elevated liver enzymes, jaundice, and fever are the most common symptoms. They can lead to hepatocellular lesions with subsequent liver necrosis. In most cases, patients occur after the identification and suspension of the pathogen. Consolidation of information on hepatotoxicity shows that several groups of drugs have more evidence that they are substances that cause liver toxicity.

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