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# Drug induced liver toxicity: A comprehensive review

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# ARTICLE INFO

## ABSTRACT

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Keywords Hepatic, Damage, Drugs. Drug-related problems include medication errors and adverse drug reactions. Liver is the hub of metabolic activity of the body indeed, most drugs are modified or metabolized in liver. Thus, drugs that are dependent primarily on the liver for their systemic clearance are like to have reduced elimination and subsequent accumulation, leading to excessive plasma drug concentration and adverse effects. However the effects of hepatic insufficiency on the pharmacokinetics of the drug are not consistent or predictable. The pharmacokinetic properties of an administered drug may be modified due to alterations in hemodynamics and/or in the so-called intrinsic clearance. Drugs with first pass metabolism require reduction in oral dosages; for high clearance drugs both loading and maintenance dosages need adjustment whereas for low clearance drugs maintenance dose only needs adjustment whenever possible, measuring drug level in the blood and monitoring of adverse events should be done fairly frequently. To sum up thus there are a large category of drugs used for different therapeutic indications which are toxic to the liver and kidney and thus should be cautiously administered; particularly when given at high doses or used for chronic or long term administration. This review pitches light on various drugs which induce renal and hepatotoxicity, with their mechanism of damage and clinical scenario.

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### Introduction

Drug-related problems include medication errors (involving an error in the process of prescribing, dispensing, or administering a drug, whether there are adverse consequences or not) and adverse drug reactions (any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function). Furthermore, adverse drug events can be defined as an injury — whether or not causally-related to the use of a drug.<sup>1</sup>

Liver is the hub of metabolic activity of the body indeed, most drugs are modified or metabolized in liver. Thus, drugs that are dependent primarily on the liver for their systemic clearance are like to have reduced elimination and subsequent accumulation, leading to excessive plasma drug concentration and adverse effects.<sup>2</sup> However the effects of hepatic insufficiency on the pharmacokinetics of the drug are not consistent or predictable.<sup>3</sup> Furthermore the influence of hepatic disease on different drugs can be variable, despite their sharing the same metabolic pathway. The major liver diseases include Cirrhosis, Alcohol abuse, Hepatitis A,B,C,D and E, Fattyliver, Epstein Barrvirus (infectious mononucleosis), Nonalcoholic fatty liver disease, and Hemochromatosis.

The pharmacokinetic properties of an administered drug may be modified due to alterations in hemodynamics and/or in the so-called intrinsic clearance (the magnitude of drug transporting or metabolizing capacity of the liver in the absence of hemodynamic influences). The hepatic clearance is a product of blood flow and extraction. However, these estimations are not accurate nor practical for use clinically since both hepatic perfusion and intrinsic clearance can be affected in advanced liver disease to unpredictable degrees. The situation is further complicated by shunting of blood around and within the liver, becoming a major determinant of drug disposition, in particular, first-pass extraction. Shunting is a major determinant of the disposition of high extraction compounds such as bile acids, which can be used as a measure of this parameter.

Though various tests like liver function test, indocyanine green clearance, Child Pugh score, and Meld score are used for prediction of impaired liver function, no tests can yet determine drug dosing in these patients reliably. Drugs with first pass metabolism require reduction in oral dosages; for high clearance drugs both loading and maintenance dosages need adjustment whereas for low clearance drugs maintenance dose only needs adjustment whenever possible, measuring drug level in the blood and monitoring of adverse events should be done fairly frequently.<sup>4</sup>

# Liver Damage

Liver failure occurs when liver cells are damaged significantly and are no longer able to function. Potential causes include: 1) **Acetaminophen overdose.** Taking too much acetaminophen (Tylenol, others) is the most common cause of liver failure. Acute liver failure can occur after one very large dose of acetaminophen, or after higher than recommended doses every day for several days. The maximum amount for adults is 1 gram (1000 mg) per dose and 4 grams (4000 mg) per day; 2) **Prescription medications.** Some prescription medications, including, nonsteroidal anti-inflammatory drugs and anticonvulsants, can cause liver failure, eg: Diclofenac, Carbamazepine; 3) **Herbal supplements.** Herbal drugs and supplements, including kava,

ephedra, skullcap and pennyroyal, have been linked to liver failure; 4)

#### Hepatitis and other viruses.

Hepatitis A, hepatitis B and hepatitis E can cause liver failure. Other viruses that can cause acute liver failure include Epstein-Barr virus, Cytomegalovirus and Herpes simplex virus; 5) **Toxins.** Toxins that can cause liver failure include the poisonous wild mushroom Amanita phalloides, which is sometimes mistaken for edible species; 6) **Autoimmune disease.** A disease in which your immune system attacks liver cells, causing inflammation and injury. Autoimmune hepatitis (AIH) is one exception. This type of liver disease occurs when your immune system attacks your liver cells. AIH is a chronic condition and can result in cirrhosis (scarring) of the liver and (ultimately) liver failure.<sup>5</sup>

### Mechanism of Liver Damage

Liver is an important target of the toxicity of drugs, xenobiotics, and oxidative stress because of its unique metabolism and relationship to the gastrointestinal tract. In cholestatic disease, endogenously generated bile acids produce hepatocellular apoptosis by stimulating Fas translocation from the cytoplasm to the plasma membrane where self-aggregation occurs to trigger apoptosis. Kupffer cell activation and neutrophil infiltration extend toxic injury. Kupffer cells release reactive oxygen species (ROS), cytokines, and chemokines, which induce neutrophil extravasation and activation. The liver expresses many cytochrome P450 isoforms, including ethanol-induced CYP2E1. CYP2E1 generates ROS, activates many toxicologically important substrates, and may be the central pathway by which ethanol causes oxidative stress. In acetaminophen toxicity, NO scavenges superoxide to produce peroxynitrite, which then causes protein nitration and tissue injury. In inducible nitric oxide synthase (iNOS) knockout mice, nitration is prevented, but unscavenged superoxide production then causes toxic lipid peroxidation to occur instead. Microvesicular steatosis, nonalcoholic steatohepatitis (NASH), and cytolytic hepatitis involve mitochondrial dysfunction, including impairment of mitochondrial fatty acid beta-oxidation, inhibition of mitochondrial respiration, and damage to mitochondrial DNA. Induction of the mitochondrial permeability transition (MPT) is another mechanism causing mitochondrial failure, which can lead to necrosis from ATP depletion or caspase-dependent apoptosis if ATP depletion does not occur fully.6

### **Drugs Causing Hepatic Toxicity**

Liver is the principle organ for maintaining the body's internal environment. There is currently no way to reimburse for the absence of liver function. Its major influence is on the flow of nutrients and controls the metabolism of carbohydrate, protein and fats. Drugs are an important cause of liver injury. More than 900 drugs, toxins, and herbs have been reported to cause liver injury. Drugs account for 2-5% of cases of patients hospitalized with jaundice and approximately 10% of all cases of acute hepatitis. Chronic liver disease and cirrhosis account for some 2% of mean in 17 countries with nearly 40,000 deaths per year. 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.<sup>7</sup>

# Anti-Tubercular Drugs

In antitubercular drugs, Rifampicin and INH therapy have an increased incidence of hepatitis. Rifampicin-induced cytochrome P450 enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. Isoniazid hepatotoxicity ranges from asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation. This is not caused by high plasma Isoniazid levels but appears to represent an idiosyncratic response. 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. Isoniazid has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity. CYP1A2 is suggested to be involved in hydrazine detoxification. Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes.<sup>7</sup> Lysandro Alsina Hader et.al<sup>8</sup> conducted a study on hepatotoxicity due to rifampicin, Isoniazid and pyrazinamide in HIV states that anti HIV positive and high doses of Isoniazid were considered independent risk factors of hepatotoxicity though univariate analysis. Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity.

## NSAIDS

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a family of drugs, which taken as a group, represents one of the most frequently prescribed around the world. Thus, not surprisingly NSAIDs, along with antiinfectious agents, list on the top for causes of Drug-Induced Liver Injury (DILI).<sup>9</sup> Diclofenac hepatotoxicity is an archetype of idiosyncratic Drug induced liver injury. About 15% of 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 CYTP4502C9, diclofenac undergoes glucuronidation by UDP-glucuronosyltransferase-2B7 to form an unstable acyl glucuronide. The latter undergoes further oxidation by CYP2C8. In addition, CYP2C8 catalyzes the formation of 5-hydroxydiclofenac. Both diclofenac acyl glucuronide and benzoquinone imines derived from 5hydroxydiclofenac modify proteins covalently; hence, decreased as well as increased activity of CYP2C8 potentially increase the risk of hepatotoxicity.

Zeynab Kh. El- Maddawy and Ibrahim M. El-Ashmawy conducted a study on Hepato-Renal and Hematological Effects of Diclofenac Sodium in Rats,<sup>10</sup> they found that diclofenac sodium at dose of 13.5 mg / kg b.wt induced a significant decrease in Hb, PCV, RBCs and WBCs values. It could be concluded that administration of diclofenac sodium at high dose induced some adverse effects on hematological, biochemical, oxidative parameters as well as histology of liver and kidney. That could be attributed to oxidative stress induced by the drug. However, these effects were reversible.

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of chemically heterogenous medications used widely in the therapy of mild-to-moderate pain and inflammation. Aspirin and acetaminophen are technically NSAIDs and they can cause liver injury, but the injury is due to intrinsic toxicity and usually associated with use of high doses or overdoses. The liver injury caused by typical NSAIDs is, in contrast, most likely idiosyncratic. Clinically apparent liver injury from NSAIDs is rare (~1-10 cases per 100,000 prescriptions) and typically presents as acute hepatitis within 1 to 3 months of starting the medication. The apparent mechanism by which almost all NSAIDs produce hepatic injury is idiosyncrasy rather than intrinsic toxicity. The main exceptions to this are acetaminophen and aspirin, which case a dose related injury. Although many cases of NSAID related liver injury demonstrate evidence of an immunologic cause, there is evidence that toxic metabolites contribute to the liver injury for some NSAIDs. Severity ranges from asymptomatic elevations in serum aminotransferase levels, hepatitis with jaundice to fulminant liver failure and death. Complete recovery is expected after stopping the drug.<sup>11</sup>

NSAIDs exhibit a broad spectrum of liver damage ranging from asymptomatic, transient, hyper-transaminasemia to fulminant hepatic failure. However, under-reporting of asymptomatic, mild cases, as well as of those with transient liver-tests alteration, in conjunction with reports noncompliant with pharmacovigilance criteria to ascertain DILI and flawed epidemiological studies, jeopardize the chance to ascertain the actual risk of NSAIDs hepatotoxicity. Several NSAIDs, namely bromfenac, ibufenac and benoxaprofen, have been withdrawn from the market due to hepatotoxicity; others like nimesulide were never marketed in some countries and withdrawn in others. Indeed, the controversy concerning the actual risk of severe liver disease persists within NSAIDs research.<sup>9</sup>

### Anti-Retroviral Drugs

Several anti-retrovirals have been reported to cause fatal acute hepatitis; they most often cause asymptomatic elevations of transaminases. 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). Mark S. Sulkowski carried out study on drug- Induced Liver Injury Associated with Antiretroviral Therapy that Includes HIV-1 Protease Inhibitors,<sup>12</sup> showed that a person with significant liver disease may have a higher serum concentration of hepatically metabolized Protease Inhibitors (PIs); however, to date, there are few data that firmly link high concentrations of PIs and hepatotoxicity. Among specific PIs, the use of full-dose ritonavir appears to be associated with the highest risk of developing LEEs. However, recent data suggest that the use of low dose ritonavir to pharmacologically boost other PIs, such as lopinavir, is not associated with greater risk of liver injury compared with other PIs, such as nelfinavir or indinavir. Other PIs (e.g., indinavir and atazanavir) are associated with a benign increase in unconjugated bilirubin in HIV-infected patients, because of their direct inhibition of hepatic UTG activity.

# Anti-Hyperlipidemic Drugs

The anti-hyperlipidemic 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 aminotransferases is common. The notion that ezetimibe may have less risk of hepatotoxicity has recently been challenged and it may not be a "safe alternative" to statins in patients with pre-existing liver disease.<sup>13</sup> Atorvastatin-related hepatotoxicity has been associated with a mixed pattern of liver injury typically occurring several months after the initiation of the medication. Mixed hepatic injury in hepatocellular and cholestatic patterns has also been noted with the use of Lovastatin. This type of liver injury covers damage with varying proportions of cytotoxic and cholestatic involvement. Direct effect or productions by enzyme-drug adduct leads to cell dysfunction, membrane dysfunction cytotoxic T-cell response. One reported case in which a liver biopsy was done revealed histologic findings of centrilobular necrosis and cholestasis with a mixed inflammatory infiltrate.<sup>7</sup> Statins and Hepatotoxicity: Focus on Patients with Fatty Liver <sup>14</sup> study concluded by Naga Chalasani states that unquestionably, statins are extremely valuable for treating human disease and they are here to stay. The available data indicate that statins are remarkably safe from a hepatic standpoint, but there are several issues related to their usage in humans that require further research and scrutiny.

## Anesthetic Agents

These are the agents who cause reversible loss of pain and sensation. These are of two types, local anesthetics and general anesthetics. These agents cause hepatocellular damage (Direct toxicity and immune mediated hypersensitivity) and interfere with bilirubin metabolism and cause cholestasis.<sup>7</sup> Halothane was introduced into use as an anesthetic in 1956, and replaced ether as the anesthetic of choice. Within two years, isolated case reports of severe hepatitis were being reported. 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. The second type of halothane-mediated hepatotoxicity is type II halothane hepatitis. The incidence of this type of hepatotoxicity after halothane administration is one case per 10000-30000 adult patients. The probable mechanism is most likely an immunemediated hepatotoxicity; antibodies are against modified liver microsomal proteins on hepatocyte surface.<sup>7</sup> Anti-Epileptic Drugs

Liver injury associated with antiepileptic drugs is well recognized. The frequency of the most common antiepileptic drugs 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 antiepileptic drugs are not clear. Reactive metabolites from antiepileptic drugs can, in some cases, lead to direct cytotoxicity and liver cell necrosis, whereas in other cases this may lead to neoantigen formation inducing immunoallergic mechanisms.<sup>7</sup> Carbamazepine (CBZ) will leads to increase in gamma glutamyl transferase and lesser extent in alkaline phosphatase (ALP), due to its enzymeinducing properties. CBZ may lead to cholestatic and hepatochepatocellular injury, even granuloma formation in the liver. The metabolism of carbamazepine is thought to play an important role in the pathogenesis of CBZ.<sup>6</sup> Valproic acid (VPA) is a potent antiepileptic drug and is also widely used. Usually it is well tolerated, but begin elevation of any liver enzyme may occur in as many as 20% of patients. There is a hypothetical mechanism of toxicity of VPA. This hypothesis oxidation of the endogenous lipids. VPA forms an ester conjugate with carnitine that may lead to secondary carnitine deficiency. Several lines of indirect evidence and in vitro studies indicate that the thioester derivative of VPA and coenzyme A may exist as a metabolic intermediate in liver tissue. Depletion of coenzyme A or VPA CoA ester itself could responsible of inhibition for mitochondrial metabolism.<sup>7</sup>

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.<sup>7</sup> According to Syed Nizamuddin Ahmed and Zaeem A. Siddiqi,<sup>15</sup> with the ever-increasing indications and markets for AEDs, the need for a better understanding of their pharmacokinetics and potential toxicity is imperative. Following are some points to consider when patient is on antiepileptic treatment; 1. There is no proven value of routine blood testing for monitoring liver functions in asymptomatic patients. They recommend a baseline test to identify an existing problem; 2. The presence of underlying liver disease may require dose adjustment and not necessarily the discontinuation of the medication. Exceptions apply to FBM, VPA and possibly CBZ; 3. In most established cases hepatic toxicity is idiosyncratic or part of a hypersensitivity reaction. Dose dependent hepatotoxicity is rare and usually reversible with prompt discontinuation of the offending agent.

# **Anti-Hypertensive Drugs**

Antihypertensives are a relatively uncommon cause of liver damage. Symptoms vary depending on the degree of exposure and hence extent of the liver damage or injury. Mild liver damage may cause few if any symptoms whereas severe damage can ultimately result in liver failure. Symptoms may be acute, subacute or chronic depending on the severity of the exposure. Factors such as age, race, gender, overall health and underlying liver problems may also influence a person's risk of developing liver problems and the severity of the symptoms.<sup>1</sup> Patients receiving Methyldopa have been reported with rises of serum transaminases and according to various reports is found in two to 10 % of patients receiving the drug. 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. In vitro studies have shown that the drug is metabolized by both human and rat liver microsomes, by the cytochrome P450 system, with consequent covalent binding to cellular macromolecules. This covalent binding is inhibited by a variety of agents, including glutathione, ascorbic acid and superoxide dismutase consistent with the oxidation of methyldopa by cytochrome P450generated superoxide anions to a reactive quinone or semiquinone.

According to Tauseef Ali et.al<sup>17</sup> Alpha-methyldopa is a pro-drug, the active metabolite, alpha-methylnorepinephrine, lowers blood pressure by stimulating central inhibitory alphaadrenergic 2 receptors and possibly by reduction of plasma rennin levels. Rarely, this could also cause sexual dysfunction, gynecomastia, thrombocytopenia, hemolytic anemia, leukopenia, hyperprolactinemia, cholestasis, hepatitis and hepatocellular injury and SLE like syndrome. The mechanism for hepatitis is not fully understood, it is thought to be related to the abnormal transformation of alpha-methyldopa by cytochrome P450 and an immune reaction to the resultant metabolite. The hepatocellular damage caused by alphamethyldopa is usually reversible on discontinuation of the medication.

#### Neuroleptic or 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.<sup>7</sup> 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 cholestasis. The of the hepatocellular mechanism phenothiazines-induced cholestatic disease remains uncertain.<sup>18</sup> Another drug 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-oxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individual.

Risperidone and quetiapine are two of the most commonly used atypical antipsychotic agents. Drug-induced cholestasis is the blockage of the flow of bile from the liver caused by a drug. This can occur by the agent selectively blocking uptake of bile components, interfering with the canalicular excretions of bile, or destroying components necessary for bile flow. Oftentimes, ALT and AST levels are normal or only mildly elevated in cholestatic injury.<sup>8</sup> There are reports of transient liver biochemistry abnormalities associated with olanzapine but the mechanism, underlying this complication is not known. There is a case report of young man who developed transient severe abnormal liver biochemistry with hepatosplenomegaly and cholestatic jaundice, after receiving olanzapine.<sup>8</sup> Clozapine is an atypical neuroleptic; an increase in alanine transaminase (ALT), which was mild and transient, occurred in 37% of recipients. The possible mechanism of hepatotoxicity is still unclear.7

Katie F.M. Marwick, MBChB et.al<sup>19</sup> carried out a review on Antipsychotics and Abnormal Liver Function Tests concluded that the most likely LFT to be abnormal in those receiving regular antipsychotics are transaminases, although others can also be affected. Most LFT abnormalities arise within 6 weeks of starting an antipsychotic, suggesting monitoring at approximately this interval may be useful. With continued treatment, most LFT abnormalities do not worsen and some resolve. Rarely, antipsychotics have been associated with severe and occasionally fatal hepatic injury. However, important candidate mechanism is an increased risk of metabolic syndrome leading to nonalcoholic fatty liver disease. Obesity and other features of the metabolic syndrome have been found to be strongly associated with unexplained transaminase elevations in other populations and weight gain to be strongly associated with transaminase increases during initiation. According to Khaled selim and Neil Kaplowitz<sup>2</sup> states that in phenothiazines there is a high background of asymptomatic liver test abnormalities (20%) and a lower incidence of overt liver disease (0.1%-1%). Features of hypersensitivity are seen in about half the phenothiazine cases (including positive rechallenge).

Chlorpromazine has been the most extensively studied. The clinical features appear to be accounted for by a mix of hypersensitivity reaction and metabolite toxicity. The bile ductule may be an important target, and a ductopenic syndrome is the most severe, although uncommon, consequence in experimental animals, dose-related cholestasis is induced within minutes. Chlorpromazine is a cationic amphiphile with detergent properties; it binds to and precipitates bile acids and phospholipids. It is, however, unclear if these effects are responsible for cholestasis.

#### Acetylcholinesterase

Tacrine is a reversible cholinesterase inhibitor used for Alzheimer's disease. Remarkably, in about 50% of recipients, the ALT exceeds the upper limit of normal; in 25%, the value is more than three times the upper limit, and in 2%, it is 20-fold increased The mechanism of toxicity is based on the inhibition by tacrine of acetyl cholinesterase, leading to a cholinergic celiac ganglion-induced stimulation of an afferent sympathetic pathway, resulting in vasoconstriction, leading to impaired perfusion of the sinusoids and reperfusion injury mediated by reactive oxygen metabolites. These are not mutually exclusive hypotheses in that the former mechanism may sensitize to the latter. Thus, tacrine undergoes high extraction, suggesting that periportal hepatocytes may take up a large proportion of the drug; the uncoupling effect would increase respiration and O<sub>2</sub> consumption in periportal hepatocytes, thus limiting O<sub>2</sub> availability in the more distally perfused perivenular cells; superimposition of decreased O<sub>2</sub> delivery as a result of the effect on the microcirculation would further limit O<sub>2</sub> in the perivenular.7

Paul b whatkins et.al<sup>21</sup> conducted a study Hepatotoxic administration in Patients with Effects of Tacrine Alzheimer's Disease Among the 2446 patients who received tacrine in clinical trials, ALT levels greater than the upper limit of normal (ULN) occurred on at least one occasion in 1203 patients (49%), ALT levels greater than three times the ULN occurred in 621 patients (25%), and ALT levels greater than 20 times the ULN occurred in 40 patients (2%). The elevated ALT levels were generally asymptomatic and occurred more frequently in women than men. The mean time from initiation of tacrine treatment to first ALT level greater than three times the ULN was 50 days, and 90% of all initial ALT levels greater than three times the ULN occurred during the first 12 weeks of treatment. Of 145 patients who discontinued tacrine treatment because of an ALT level greater than three times the ULN and were rechallenged, 127 (88%) were able to resume long-term therapy with the drug. In all instances, discontinuing tacrine completely reversed elevations in ALT levels, and no deaths related to hepatotoxicity occurred. These data suggest that the potential for serious hepatic toxicity can be reduced through careful monitoring of ALT levels in patients who may benefit from tacrine.

#### **Anti-Depressants**

Most tricyclic antidepressants are potentially hepatotoxic. Although other tricyclics (including amitriptyline, desipramine, doxepin) rarely cause liver disease the reported cross-reactivity should preclude their use when sensitivity to one has been suspected. Amineptine-induced liver disease is mainly cholestatic, although moderate necrosis may be seen. The compound has a heptanoic acid side chain. - oxidation, leading to inhibition of medium- and short-chain fatty acid boxidation. Thus, both drugs are converted by P450 to reactive metabolites that can induce a hypersensitivity reaction in genetically susceptible individual. Imipramine can induce a cholestatic jaundice that generally is not progressive.<sup>7</sup>

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.<sup>7</sup> Cosmin Sebastian Voican. et.al<sup>22</sup> circumstances that cases of lifethreatening hepatic failure and death have been reported in patients treated with antidepressants. For the older drugs, notably MAO inhibitors, tricyclic/ tetracyclic antidepressants, fluoxetine, and mianserin, data are scarce because the results of clinical trials are not available, and only case reports have been published. With more recent drugs, such as duloxetine, venlafaxine, bupropion, and agomelatine, data from both clinical trials and published case reports are available. In patients with a concomitant increase in ALT and bilirubin, treatment continuation (particularly of imipramine/desipramine, amitriptyline, paroxetine, trazodone or agomelatine) despite hepatotoxicity could lead to severe hepatic failure or chronic hepatocellular dysfunction that may progress to liver cirrhosis. Although an infrequent event, DILI from antidepressant drugs may be irreversible, and clinicians should be aware of it. Aminotransferase surveillance is the most useful tool for detecting DILI, and prompt discontinuation of the drug responsible is essential.

#### Conclusion

Seeing the status of drug-induced renal and hepatotoxicity as the foremost causes of kidney and liver damage. The incline of toxic drugs is enormous and a comprehensive reporting is tough. To sum up thus there are a large category of drugs used for different therapeutic indications which are toxic to the liver and kidney and thus should be cautiously administered; particularly when given at high doses or used for chronic or long term administration. This review pitches light on various drugs which induce renal and hepatotoxicity, with their mechanism of damage and clinical scenario.

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