Review

Liver and substance use disorders

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Liver disorders in substance abusers

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Abstract

Substance use disorders are a global health problem with detrimental effects on one's health, wealth, and stealth. It includes the use of prescribed medications or the use of illicit drugs in excess amounts or for excess durations associated with complex neuropsychiatric and/or physical manifestations. It affects every organ in the body, and the liver is no exception to the deleterious effects of substance abuse. The mechanism of liver injury varies from agent to agent and may include direct toxic effects, oxidative stress, and inflammatory responses. The hepatic involvement ranges from asymptomatic liver enzyme elevation and fatty liver disease to hepatitis, liver failure, and cirrhosis. Alcohol, the most frequent agent implicated in substance use disorder, is also a prototype hepatotoxin, capable of inducing the whole spectrum of liver diseases. Cigarette smoke contains numerous harmful chemicals, including carcinogens, which can induce liver injury, fibrosis, and HCC. Cocaine, particularly in acute overdose, can result in ischemic hepato-necrosis, while it can also result in clinically inapparent transaminasemia. Marijuana and opiates, despite being associated with numerous deleterious effects, are rarely implicated in clinically apparent liver injury. Individuals with substance use disorder are also prone to viral hepatitis and hepatic insults secondary to hypotension, hypoxia, and other systemic ailments. Liver transplant candidacy in individuals with substance use disorder is a highly complex arena, with guidelines balancing abstinence requirements against evolving evidence on outcomes. This review article provides a thorough analysis of the hepatotoxic repercussions stemming from the agents commonly implicated in substance abuse disorders.

Keywords: Alcohol; cocaine; DILI; hepatotoxicity; liver injury; marijuana; sedatives; stimulants; substance abuse; tobacco.

Introduction

Substance use disorders (SUD) refer to the use of legal or illicit substances in excess amounts or for prolonged durations, associated with complex neuropsychiatric and physical manifestations. The global prevalence of SUD is estimated to be 2.2%, and alcohol alone contributes to 1.5%; however, marked regional variations exist.[1] As per the 2022 National Survey on Drug Use and Health, United States, 48.7 million, or 17.3%, individuals above 12 years of age had a SUD in the past year, which includes 29.5 million with alcohol use disorder (AUD), 27.2 million with a drug use disorder (DUD), and 8.0 million with combined AUD and DUD.[2] SUD affects health, personal and professional performance, and regional, national, and global socioeconomic and crime indices. The frequently implicated agents in SUD are alcohol, followed by tobacco, marijuana, cocaine, opiates, stimulants, sedatives, and inhalants.[2] These 'substances' are often associated with direct injury or health hazards involving one or multiple organ systems. In addition, SUDs are often linked to mental health issues not only as an underlying condition but also as a risk factor. Similarly, the incidence and prevalence of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection, are reportedly higher in people with SUDs.

The liver is highly susceptible to toxic injury owing to its high metabolic activity, extensive hepatobiliary transporter mechanisms, and highly vascular nature. Hepatotoxicity can result from direct or reactive metabolite toxicity, adaptive immune response, mitochondrial toxicity, and/or oxidative stress.[3] Toxicity is more frequently idiosyncratic and immune-mediated and less often dose-dependent and predictable. The hepatic injury may follow a hepatocellular, cholestatic, or mixed pattern.[4] Alcohol, the most frequent agent implicated in SUD, also has the most well-described hepatotoxicity. Alcohol is the most common cause of liver disease in many parts of the world. Alcohol-related cirrhosis and hepatocellular carcinoma (HCC) contribute to roughly 1% of global mortality.[5] The hepatotoxic effects of agents of abuse other than alcohol, though described, have garnered less attention in literature and clinical practice. This review intends to summarize the hepatotoxic effects of substances of abuse. The methodology involved conducting thorough searches on 'Google' and 'PubMed' and reviewing published medical literature concerning various substances of abuse such as 'alcohol,' 'tobacco,' 'cocaine,' 'cannabis,' 'marijuana,' 'opiates' etc., AND 'hepatotoxicity' or 'liver injury.' The authors independently analyzed the publications in English, and related data were drawn and summarized, while publications in other languages were excluded. Table 1 summarizes the deleterious effects of commonly encountered substances of abuse on the liver.[6,7]

Alcohol

The liver is the primary site of alcohol metabolism and involves three pathways (Fig. 1). The most important is the alcohol dehydrogenase pathway, which operates in the hepatocyte cytoplasm, converting ethanol to acetaldehyde and generating reduced nicotinamide adenine dinucleotide (NADH) as a byproduct. The second pathway involves the microsomal ethanol-oxidizing system (MEOS) in the smooth endoplasmic reticulum, mediated by cytochrome P450 2E1 (CYP2E1) enzyme.

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Table 1. Summary of substance use disorder associated liver injury

Ethanol	Alcohol associated liver diseases: steatosis, steatohepatitis, alcoholic hepatitis, cirrhosis, HCC
Tobacco	Contributes to progression of underlying liver disease, fibrosis, cirrhosis, HCC
Cocaine	Well known cause of acute liver injury, but only with overdose‡
	Most frequently elevated liver enzymes, rarely severe hepatocellular injury with necrosis.
Marijuana/cannabis	Unlikely cause of CALI‡
Opiates	Unlikely cause of CALI‡
	No-DILI-concern: Morphine, codeine, oxycodone*
	Ambiguous-DILI-concern: Hydromorphone*
Benzodiazepines	Ambiguous-DILI-concern: Diazepam, lorazepam, oxazepam*
	Less-DILI-concern: Alprazolam, clonazepam, chlordiazepoxide*
	Possible/probable rare cause of CALI: Alprazolam, clonazepam, chlordiazepoxide, diazepam, lorazepam‡
	Unlikely cause of CALI: Oxazepam, temazepam, clobazam‡
	Bentazepam has been associated with hepatitis and severe DILI
Barbiturates	Less-DILI-concern*
	Unlikely cause of CALI‡
	May cause DRESS syndrome-related hepatic changes
Z-class sedatives	No-DILI-concern: Zaleplon*
	Ambiguous-DILI concern: Zolpidem, zopiclone*
	Unlikely cause of CALI‡
Amphetamines (ATS)	No-DILI-concern: Methamphetamine, dextroamphetamine*
	Less-DILI-concern: Amphetamine, methylphenidate*
	MDMA: well-established cause of liver injury, but severe only with high doses‡
	Methylphenidate: Probable cause of CALI at high doses‡
Phencyclidine	Rarely causes severe hepatocellular injury with necrosis
	Probable cause of CALI but only at high doses‡
Inhalants	Halogenated hydrocarbons: Idiosyncratic hepatotoxicity, DILI
	Aromatic hydrocarbons: Deranged liver enzymes

‡LiverTox: Clinical and research information on drug-induced liver injury; *https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset; DILI: Drug-induced liver injury; CALI: Clinically apparent liver injury.

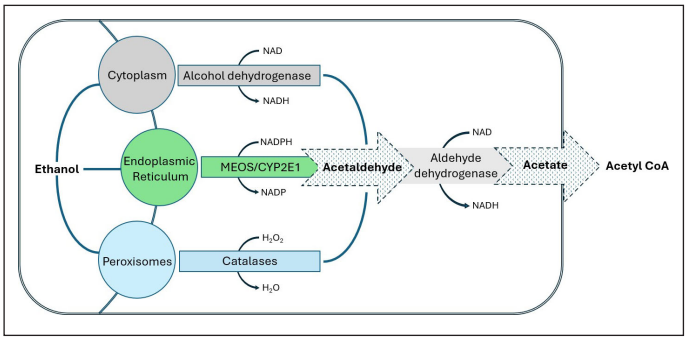

Figure 1. Metabolism of ethanol.

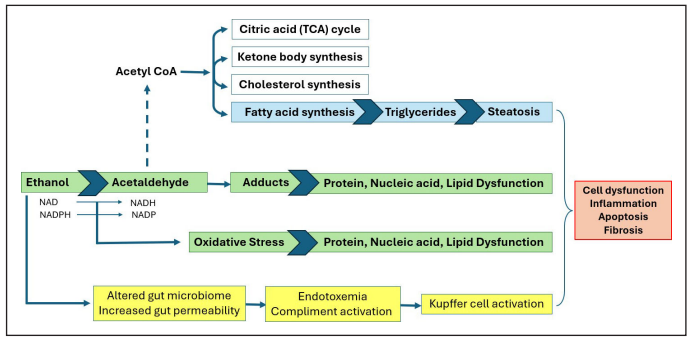

Figure 2. An overview of mechanisms involved in alcohol-induced liver injury.

CYP2E1 is an inducible enzyme and is upregulated with chronic alcohol use, generating acetaldehyde from alcohol as well as reactive oxygen species (ROS). The peroxisomal catalases mediate the third metabolic pathway and generate acetaldehyde. Irrespective of the pathways, the mitochondrial aldehyde reductase enzyme converts acetaldehyde to acetate, which diffuses into the circulation; this reaction generates another molecule of NADH.[8] The mechanism of alcohol-induced hepatotoxicity is complex and multifaceted (Fig. 2). Acetaldehyde causes cellular dysfunction by forming adducts with lipids, proteins, and nucleic acids. The altered NAD/NADH ratio and the free radicals/ROS alter the cellular redox potential, oxidative stress, injury to macromolecules, and cellular dysfunction.[9–12] Acetate, the product of oxidative ethanol metabolism, is either metabolized into carbon dioxide and water or to acetyl CoA that is shunted to ketogenesis, acid, and cholesterol synthesis. Excess fatty acid synthesis together with reduced fatty acid oxidation culminates in heightened triglyceride synthesis and fatty liver. The aldehyde adducts and oxidative stress secondary to altered redox status cause macromolecular dysfunction, hepatocyte dysfunction, and pro-

mote pathways involved in apoptosis and necrosis. Alcohol causes gut mucosal barrier dysfunction and altered gut microbiome, increased mucosal permeability, endotoxemia, and activation of toll-like receptors. The inflammatory response elicited by cellular necrosis, endotoxemia, and receptor activations evokes inflammatory and complement cascades, chemotaxis, inflammatory infiltration, and further cytotoxicity, contributing to "hepatitis". The hepatic stellate cell, upon activation, generates and deposits collagen, leading to fibrosis and cirrhosis.[11,13–15]

Alcohol, the leading cause of liver disease worldwide, can cause the entire spectrum of liver diseases: steatosis, steatohepatitis, acute hepatitis, cirrhosis, and HCC. Alcoholic hepatitis and cirrhosis rank among the leading indications for liver transplantation worldwide. Hepatic steatosis is the earliest, commonest, and likely the most predictable manifestation of ethanol hepatotoxicity, seen in about 90% of heavy alcohol users. Steatosis is largely reversible with abstinence; however, with continued ethanol use, it progresses to steatohepatitis, fibrosis, and cirrhosis. Acute alcoholic hepatitis is a noteworthy manifestation of excess use as severe cases carry a poor prognosis. Acute-on-chronic liver failure, resulting from superadded alcoholic hepatitis on cirrhosis, has the most dismal prognosis. The factors that might influence the onset and severity of alcoholic liver disease include female sex, obesity, smoking, and concomitant viral, hereditary, drug-induced, or infectious liver disease.[14,16,17] The risk of HCC in alcoholic cirrhosis varies across populations; the most recent data estimates the cumulative risk as 3% and 9% at 5 and 10 years, respectively.[18]

In the past and even to date, many recommend a period of sobriety, typically six months before transplantation. Though questionable, the rationale behind the '6-month rule' is to negate the risks related to recidivism and allow possible improvement in liver function following abstinence, but it is not backed up by adequate scientific evidence.[19] In severe alcoholic hepatitis not responding to medical management, the survival rate at six months is only around 30%, so strict adherence to the 6-month rule will deny timely treatment to this subgroup of patients. Hence, liver transplants are increasingly performed in selected patient groups before this window. Studies comparing early (<6 months abstinence) and per policy (>6 months abstinence) liver transplants have reported comparable survival, alcohol relapse rates, and mortality rates.[20,21] The key to early transplant success across all these published studies is the stringent patient selection criteria: severe alcoholic hepatitis refractory to medical therapy, assessed by an addiction specialist as having a favorable psychosocial profile, no prior known liver disease, including alcoholic hepatitis.[22] Though these studies have exposed the fallacy of the 6-month rule, it remains yet to be proven if the positive benefits of early liver transplant will outweigh its risks across the spectrum of transplant-requiring alcoholic liver diseases without having deleterious impacts on organ availability.

Tobacco

The hepatotoxic effects of tobacco have garnered little attention, likely overshadowed by its deleterious cardiopulmonary effects and carcinogenic potentials. Tobacco is often smoked; smokeless tobacco use is less frequent and includes chewing and sniffing. Cigarette smoking, the most frequent form of tobacco use, generates about 7000 chemicals, 250 of them hazardous, including 69 carcinogens.[23] These chemicals' direct and indirect effects, compounded with the immunological and oncogenic effects, contribute to hepatotoxicity. Smoking generates carcinogens such as tar, vinyl chloride, nitrosamines, and hydrocarbons, and it is the major source of 4-aminobiphenyl, a hepatic carcinogen. These carcinogens induce nucleic acid damage and mutations predisposing to atypical cell growth, suppress tumor suppressor genes, and cytotoxic T-cell responses to atypical cells.[24] Smoking generates proinflammatory cytokines and free radicals/oxidative stress, leading to hepatocyte injury and stellate cell activation. Activated stellate cells stimulate the synthesis of type 1 collagen, platelet-derived growth factor (PDGF), fibroblastic growth factors (FGF), and insulin-like growth factor (IGF), and upregulate kappa B nuclear factor (NF-kB) and transforming growth factor-β (TGF-β) pathways, all predisposing to fibrosis and carcinogenesis. The activated stellate cells are a further source of proinflammatory cytokines.[24,25] Smoking-induced carboxyhemoglobinemia and subsequent hypoxia predispose to polycythemia, increased red cell turnover, increased intestinal iron absorption, and secondary iron overload, again promoting oxidative stress and hepatocyte injury.[26]

Cigarette smoking has been linked to the onset and progression of nonalcoholic fatty liver disease (NAFLD).[27,28] In experimental models, nicotine has resulted in the inactivation of AMPK, the key negative regulator of fatty acid and cholesterol synthesis.[29] Cigarette smoking-induced hepatocyte injury contributes to the progression from simple steatosis to steatohepatitis.[28] Smoking is associated with cirrhosis, worse outcomes of liver transplantation, and increased risk of HCC in NAFLD or Metabolic dysfunction-associated fatty liver disease (MAFLD).[30–33] In patients with hepatitis B (HBV) and hepatitis C (HCV) infections, smoking is associated with an increased risk of fibrosis, cirrhosis, and HCC.[34–37] Smoking aggravates the progression of alcoholic liver disease to cirrhosis and HCC and acts synergistically with alcohol in liver diseases unrelated to alcohol.[38] Multiple epidemiological studies indicate the association between smoking and primary biliary cholangitis (PBC). Also, smoking is associated with an increased risk of fibrosis and cirrhosis in patients with PBC.[39,40] The meta-analysis by Lee et al.[41] concluded that current cigarette smoking is a risk factor for HCC, with a relative risk of 1.51 (95% CI, 1.37–1.67), after adjusting for HBV, HCV infections, and alcohol consumption. Smoking is associated with a lower response to treatment with interferon in HCV infection, increased vascular complications, especially hepatic artery thrombosis, following liver transplantation, and long-term deleterious effects in transplant recipients.[42,43]

Marijuana

Marijuana, extracted from the female Cannabis sativa plants, is a psychoactive substance, and its use is illegal in most of the world. However, for its analgesic and antiepileptic actions, medical cannabinoids are approved for use in a highly selected group of patients in some parts of the world. The terms marijuana and cannabis are often used interchangeably, though marijuana refers to the psychoactive extract, while cannabis refers to all products from Cannabis sativa, psychoactive and inactive.[44] The most frequent molecules in cannabis include tetrahydrocannabinol (THC), the psychoactive cannabinoid, and cannabidiol (CBD), the nonpsychoactive moiety. Cannabis undergoes extensive hepatic first-pass metabolism by the cytochrome P450 system, especially CYP2D6 and CYP3A4; the metabolites so formed undergo glucuronidation to form glucuronides excreted through urine and fecal matter.

Marijuana or cannabis use, by itself, is rarely implicated in hepatotoxicity.[14] Chronic marijuana use has been linked with elevated liver enzymes.[45,46] Liver biopsy studies dating back to 1969 demonstrated subclinical liver injury in marijuana users.[47] Marijuana has been implicated in hepatitis in case reports, mostly a diagnosis of exclusion.[48,49] Transaminase elevation was reported in trials evaluating medici-

nal cannabinoid CBD, including a few cases qualifying the definition of drug-induced liver injury.[50,51] Lo et al.[52] analyzed that high-dose CBD, >1000 mg/day, and concomitant use of antiepileptics are associated with an increased probability of transaminasemia.

Trials evaluating the impact of cannabis on liver disease have yielded divergent results to date. This is explained by the type of cannabinoid receptor involved: CB1 receptor stimulation is detrimental to the liver, while CB2 receptor activation likely confers beneficial effects. CB1 promotes progressive hepatic steatosis and fibrosis.[53] Cannabis use is reported to attenuate the antiviral immunity against HCV and is associated with worsening steatosis and fibrosis.[54] On the contrary, experimental models and epidemiological studies have reported improved outcomes in alcoholic and non-alcoholic fatty liver with cannabis.[55] Also, cannabis has been associated with improvement in hepatic encephalopathy, though further studies need to be conducted before making recommendations.[56]

Cocaine

Cocaine is one of the most addictive agents known to mankind and is associated with extensive tissue and organ damage. Hepatic involvement in acute cocaine overdosage results in ischemic hepato-necrosis, most predominant in the centrilobular and midzonal regions.[57] Hepatic biochemistry reveals a dramatic increase in transaminases and lactate dehydrogenase levels and coagulopathy followed by hyperbilirubinemia 2–3 days later. If the insult is removed, the liver injury resolves spontaneously, with normalization of laboratory values in 1–2 weeks.[7,58] In humans, about 90% of cocaine is metabolized by plasma cholinesterase and tissue esterase to nontoxic metabolites. About 10% undergo CYP450-mediated metabolism to generate the toxic metabolite, norcocaine, the role of which in human cocaine hepatotoxicity is unclear.[7,59] Chronic cocaine use may be associated with asymptomatic elevation in transaminase levels. N-acetyl cysteine is found to be beneficial in cocaine-induced hepatotoxicity.[58]

Opiates

Opioid overuse claims more deaths than any other drug overdose; over 75% of drug overdose deaths in the United States in 2021 involved opioids.[60] The frequently implicated opiates include the prescription drugs morphine, oxycodone, hydrocodone, and methadone, together with the synthetic opioid fentanyl and the illegal opioid heroin.[61] Opiates, though associated with a wide variety of systemic effects and adverse effects, are included under drugs with no or minimal concern for clinically apparent liver injury.[62] Opiates are metabolized in the liver by phase 1 or phase 2 reactions; hence, theoretically, opiate abuse could lead to hepatic injury. Experimental studies in rats suggest opiate hepatotoxicity does occur.[63] However, in clinical practice, especially with therapeutic dosages, opiate-induced liver injury is more a myth than a reality. Most liver diseases in individuals with opiate use disorder are attributed to the concomitant use of hepatotoxic agents (e.g., alcohol) or related to hepatotropic viral infections (e.g., HBV, HCV) or therapeutic misadventures like acetaminophen toxicity with overuse of Vicodin® or Percocet®.[64] Indirect hepatic injury can also result secondary to cardio-respiratory failure, hypotension, or hypoxia due to acute opiate intoxication. Opiate-induced sedation and constipation may precipitate hepatic encephalopathy in individuals with advanced liver disease. A literature search revealed transaminase elevation with the use of heroin and methadone but lacks convincing evidence to prove causality.[65]

Sedative Drugs

Benzodiazepines are extensively used in the treatment of insomnia, anxiety, seizures, and alcohol withdrawal. Clinically significant DILI is a rarity with benzodiazepines, though there are isolated reports of transaminase elevation and cholestasis.[66,67] Bentazepam is likely an exception to this general norm and has been reported for hepatitis, severe DILI, and even chronic liver disease.[68,69] Studies in benzodiazepine mono abusers reported no significant DILI.[70]

Barbiturates constitute another class of sedatives incriminated in sedative drug use disorders, the prototype being phenobarbital. Phenobarbital is well-documented to be linked with instances of idiosyncratic immune-allergic DILI. It is also implicated in drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome and Stevens-Johnson syndrome, both associated with hepatic dysfunction.[71] Barbiturates are also potent hepatic enzyme inducers known to alter many drugs' metabolism.

"Z drugs," the non-benzodiazepine, benzodiazepine receptor agonists, zolpidem, zopiclone, and zaleplon, constitute a novel class of sedatives. Neither the pre-marketing trials nor post-marketing surveillance evaluations have revealed any association with hepatotoxicity.[72]

Stimulant Drugs

The most frequently abused stimulants, excluding cocaine, include amphetamine-type stimulants (ATS) and phencyclidine. The ATS includes amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), and methylphenidate. Instances of hepatotoxicity with all these drugs have been reported, most frequently with MDMA. The hepatocellular pattern of DILI closely mimics ischemic hepatitis.[73] The severity of hepatotoxicity ranged from asymptomatic transaminase elevation to acute liver failure requiring transplantation.[74]

Phencyclidine (PCP or Angel dust) has simultaneous stimulant, depressant, and hallucinogenic effects. The hepatotoxic effects correlate with the development of hyperthermia, characterized by hepatic necrosis. The injury follows a hepatocellular pattern, resembling ischemic hepatitis.[75]

The leaves of Catha edulis, often called the Khat plant, are frequently chewed in Africa, especially in Yemen, for their stimulant effects. The component alkaloids, phenylalkylamines, and cathedulins are structurally related to amphetamines.[76] Khat-induced hepatotoxicity is well-reported in the literature; postulated mechanisms include direct hepatotoxicity or indirect effects of pesticides or additives contaminating the leaves or the preparations.[77] Short-term exposure has been linked with transaminitis, hepatocyte injury, and central vein congestion in animal models.[78] Animal models following prolonged Khat exposure have revealed evolution to hepatic fibrosis.[79] A literature search does reveal published data regarding khat-associated hepatitis, chronic liver disease, and cirrhosis.[77,80,81]

Inhalational Agents

Inhalational substance abuse is a growing concern worldwide. The frequently used agents include volatile solvents (petrol, paint thinners, nail polish removers, glues), gases (propane, butane, anesthetic agents, nitrous oxide), nitrites, and aerosols (deodorants, spray paints).[82] A myriad of short- and long-term adverse effects have been reported with inhalant substance abuse, including hepatotoxicity. Inhaled chloro-hydrocarbons are associated with acute hepatitis and liver failure. More

frequently, long-term use of halogenated hydrocarbons (halothane, carbon tetrachloride, and trichloroethylene) and aromatic hydrocarbons (benzene, toluene, xylene) is associated with liver injury.[83] The most frequent pattern of liver involvement is a mild elevation in liver enzymes. Anecdotal reports link chronic liver disease as well as HCC with chronic fluoro-hydrocarbon inhalation, though the association remains unproven.[84–86] Toluene is a volatile aromatic hydrocarbon in glues, paints, gasoline, thinners, and varnishes. Toluene, followed by benzene, is responsible for the deleterious effects of glue sniffing. These aromatic agents are reported to cause mildly deranged liver enzymes; serious hepatotoxicity, though reported, is infrequent.

Substance Abuse and Liver Transplant

The candidacy of an individual with SUD as a donor or recipient has remained a matter of debate ever since the introduction of liver transplant programs. It is recommended to screen transplant candidates for SUD and to provide psychosocial support and assistance. The American Association for the Study of Liver Diseases (AASLD) 2013 practice guidelines considered 'ongoing alcohol or illicit substance abuse' a contraindication for liver transplantation.[87] The guidelines from the United Kingdom, 2020, recommend that alcohol-dependent individuals who continue drinking should not be referred for a liver transplant. The guidelines recommend referral for transplant for those with >3 months of validated ethanol abstinence and for those with abstinence <3 months who are positively engaged with addiction services, provided there is a risk of liver-related mortality in <3 months.[88] However, with increasing data on positive outcomes with early liver transplants in selected cases of alcoholic hepatitis, the window of sobriety is expected to shorten or become obsolete in the future. Tobacco use is associated with increased cardiovascular mortality, hepatic artery thrombosis, oropharyngeal, and other malignancies in liver transplant recipients; hence, the AASLD 2013 guidelines recommend against tobacco consumption in liver transplant candidates.[87] Methadone maintenance therapy for opioid use disorder should not exclude or delist a patient from the liver transplant list. Per United Kingdom clinical guidelines, patients on prescribed methadone or buprenorphine may be referred for transplant, while the current use of non-prescribed addictive drugs precludes referral.[88,89] Many programs exclude or delist individuals with marijuana use disorder from the transplant registry. However, there is no convincing evidence that past or current marijuana use is associated with poor outcomes.[89] Most living donor liver transplant programs reject donors with active alcohol or illicit substance abuse.[90]

Conclusion

In conclusion, substance use disorders pose significant challenges to liver health, ranging from steatosis to cirrhosis and hepatocellular carcinoma. While alcohol remains the leading cause of liver disease worldwide, other substances also exert substantial hepatotoxic effects. The hepatotoxic effects of tobacco remain highly underrated, though it is implicated in the progression of underlying liver disease, hepatocellular carcinoma, and post-liver transplant complications. Clinically apparent liver injury is infrequent with marijuana and opiates. The deleterious hepatic effects add to an already towering list of health concerns related to substance abuse and underscore the need for comprehensive interventions addressing substance abuse. Effective screening, early intervention, and access to evidence-based treatments are crucial in mitigating the burden of substance-related liver disease on individuals and society.

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