



Hot Topic Commentary



Ketamine Hepatotoxicity: An Underappreciated Cause of Liver Damage - Analysis by RUCAM

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Introduction

Ketamine is a phencyclidine derivative primarily used as an anesthetic and analgesic, playing a key role in the treatment of acute (perioperative) pain, chronic neuropathic pain, and therapy-resistant clinical depression.¹ Although generally considered safe and effective for medical purposes, ketamine has rarely been reported to cause hepatotoxicity. However, due to its dissociative and hallucinogenic effects, recreational use—especially repeated administration—has led to an increased incidence of hepatotoxicity.

Ketamine functions as a non-competitive antagonist of the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor. This mechanism is responsible for its dissociative anesthetic properties, characterized by analgesia and altered consciousness while maintaining airway tone and respiratory drive.¹ Ketamine is commercially available as a racemic mixture, with the S-enantiomer exhibiting twice the anesthetic potency of the R-enantiomer. Conversely, the R-enantiomer has three times the antidepressant potency of the S-enantiomer.¹

Ketamine can be administered intravenously, intramuscularly, subcutaneously, intranasally, orally, and intraperitoneally. Intravenous administration is commonly used for its rapid onset, particularly in anesthesia and acute pain management. Intranasal administration is being explored for its rapid absorption and potential use in treating depression. Oral administration, despite its lower bioavailability due to first-pass metabolism, is under investigation for its potential benefits in chronic pain and depression.¹

Epidemiology of ketamine medical use

Ketamine is used across a wide age range; in adult emergency department settings, patients receiving ketamine have been reported to range in age from 20 to 97 years. Males are

more likely to receive ketamine in both pediatric and adult settings. Ethnoracial representation in ketamine medical use indicates that the majority of patients receiving ketamine in hospital-based settings are Caucasian.² In critical care, a retrospective cohort study found that continuous ketamine use in mechanically ventilated adults in the United States increased significantly from 0.07% in 2008 to 1.1% in 2018, with substantial variability among hospitals.²

Epidemiology of ketamine recreational use

In the United States, there has been a significant increase in recreational ketamine use, exposures, and seizures. From 2006 to 2019, self-reported past-year non-medical ketamine use increased, peaking at 0.9% in late 2019. The rate of exposures reported to poison centers also rose from 1991 through 2019, stabilizing at 1.1 exposures per 1,000,000 population by 2014.² A study using data from the National Survey on Drug Use and Health (2015–2019) estimated that 0.13% of U.S. adults used ketamine, with a higher prevalence among males and individuals with past-year drug use or sexual minority status. Users spanned various age groups, with the highest use among those aged 20–29 years.² From 2019 to 2021, there was an 81.1% increase in reported ketamine exposures, with a significant proportion involving poly-drug use—raising the risk of severe adverse effects, including hepatotoxicity and death.³ Globally, ketamine's popularity as a recreational drug has grown, particularly in Asia, where it is commonly used in dance and nightclub settings.⁴

Ketamine metabolism

Ketamine undergoes extensive metabolism in the liver. The primary metabolic pathway involves N-demethylation to form norketamine, catalyzed mainly by cytochrome P450 (CYP) enzymes. Norketamine is further metabolized through hydroxylation of the cyclohexanone ring, forming hydroxynorketamine and dehydronorketamine via CYP2B6 and CYP2A6. These metabolites, particularly hydroxynorketamine, have been shown to possess pharmacological activity, including potential antidepressant effects.¹

Data analysis and review

The Roussel Uclaf Causality Assessment Method (RUCAM) is a published tool used to objectively and quantitatively assess causality in cases of suspected drug-induced liver injury (DILI)

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and herb-induced liver injury.⁵ Despite the extensive literature on ketamine-associated DILI, no studies to date have explicitly used RUCAM to investigate this relationship and establish causality. A total of 27 studies have explored ketamine-associated DILI, as summarized in Tables 1 and 2.^{6–31} Cotter *et al.* conducted a retrospective case series identifying 14 cases with 21 hepatobiliary adverse events, including liver enzyme elevation, biliary dilation with liver cirrhosis, and cholangitis, associated with repeated or continuous medically supervised ketamine administration.⁶ These findings suggested a significant association between prolonged ketamine use and liver injury, particularly in the context of chronic pain management. Noppers *et al.* reported three cases of DILI following repeated ketamine treatment for chronic pain, with elevated liver enzymes normalizing after cessation of ketamine.⁷ Wong *et al.* conducted a cross-sectional survey of chronic ketamine abusers, finding a 9.8% prevalence of liver injury. All cases had bile duct injury and significant liver fibrosis (Table 1).¹¹ Without RUCAM, these studies may not have adequately excluded other potential causes of liver injury, leading to possible misattribution. Other factors that could have contributed to liver injury in these studies include pre-existing liver diseases, comorbidities (such as COVID-19 or conditions requiring ICU admission and sedation), concurrent use of hepatotoxic drugs, alcohol consumption, and metabolic conditions.

Although no studies reported RUCAM scores, we reviewed all 17 reported cases and calculated scores for those with sufficient data using the most updated RUCAM guidelines. This information is presented in Table 1. Among these cases, eight had scores > 8, indicating a highly probable causal relationship, while an additional three cases had scores of 5–7, suggesting a probable relationship. Notably, in some cases listed in Table 1, other drug and non-drug causes of liver injury were not excluded; these cases are marked with an asterisk. Other non-clinical studies addressing ketamine hepatotoxicity are listed in Table 2, though RUCAM scores were not calculated for these as they were non-clinical studies.

Mechanism of ketamine-induced liver injury

Ketamine can cause hepatocellular damage through several mechanisms, primarily via mitochondrial dysfunction and apoptosis. It has been shown to impair mitochondrial function, particularly by inhibiting mitochondrial complex I activity. This inhibition reduces ATP production and decreases mitochondrial membrane potential, leading to cellular energy deficits and hepatocellular injury. Additionally, ketamine induces apoptosis in hepatocytes through activation of the Bcl-2-associated X protein-mitochondria-caspase protease pathway. This process involves the translocation of Bcl-2-associated X protein to the mitochondria, the release of cytochrome c into the cytoplasm, and the subsequent activation of caspases-9, -3, and -6, culminating in DNA fragmentation and cell death. Ketamine also disrupts the cytoskeleton of hepatocytes by suppressing calcium mobilization and mitochondrial function, which impairs hepatic cellular integrity and function (Fig. 1).⁹ The mechanism of biliary injury remains unclear. However, one proposed theory suggests that the blockage of the ketamine-induced N-methyl-D-aspartate receptors in smooth muscle cells leads to bile accumulation and increased contraction of the sphincter of Oddi, resulting in functional obstruction and cholestasis.¹⁰

When cells undergo necrosis during DILI, as seen with ketamine, they lose membrane integrity, causing intracellular molecules known as damage-associated molecular patterns to spill into the extracellular environment. These molecules act as pro-inflammatory signals, activating local immune

cells and initiating a drug-induced inflammatory response. This response shifts immune cells toward a pro-inflammatory state, triggering cytokine release, which amplifies and sustains the inflammatory cascade. If unchecked, this process exacerbates tissue injury, potentially leading to fibrosis and, eventually, cirrhosis.⁹

While most cases of ketamine-induced liver injury appear to be due to direct toxicity, some cases may be idiosyncratic, as evidenced by variability in patient responses, timing, and occurrence after repeated use.³² In a case series of patients with complex regional pain syndrome type 1, one patient exhibited elevated liver enzymes on the first day of their second ketamine infusion, despite tolerating the initial course without incident.⁷

Acute hepatotoxicity

Ketamine-induced liver injury can occur in both acute and chronic settings. However, acute liver damage from ketamine use is relatively rare. It typically presents as transient elevations in liver enzymes—alanine and aspartate aminotransferases, alkaline phosphatase, and γ -glutamyl transferase—shortly after administration. This pattern is commonly observed with short-term, controlled dosing and has consistently been shown to be reversible upon drug discontinuation. For example, Cotter *et al.* reported transient liver enzyme elevations in patients receiving repeated or continuous ketamine infusions for chronic pain, with resolution following drug cessation.⁶ Similarly, in a study by Noppers *et al.*, three patients developed dose-dependent hepatotoxicity, characterized by elevated liver enzymes during or shortly after repeated ketamine infusions for chronic pain management. Symptoms included itching, rash, fever, and modestly increased eosinophils. Liver enzymes returned to normal within two months after discontinuation of ketamine.⁷ To date, no cases of chronic hepatitis or liver failure following ketamine cessation have been reported. All cases reviewed in the literature either documented the resolution of abnormal liver function or lacked long-term follow-up. Based on current evidence, acute ketamine exposure predominantly leads to hepatocellular injury, while chronic use primarily results in biliary injury.

Chronic hepatotoxicity

Chronic ketamine use is more strongly associated with severe liver damage, particularly hepatobiliary injury, including bile duct dilatation and cholangiopathy. Wong *et al.* reported a 9.8% prevalence of liver injury among chronic ketamine users, characterized by abnormal cholestatic patterns, bile duct injury, and, in some cases, significant liver fibrosis.¹¹ Cotter *et al.* identified hepatobiliary adverse events in patients receiving repeated or continuous medically supervised ketamine administration. Among the 14 cases reviewed, one patient developed biliary dilation with liver cirrhosis.⁶ Seto *et al.* performed MRCP imaging on individuals with at least six months of recreational ketamine use and observed diffuse extrahepatic biliary dilatation, fusiform extrahepatic biliary dilatation, and intrahepatic ductal changes without extrahepatic involvement. This study highlighted that ketamine-associated cholangiographic anomalies were reversible upon drug discontinuation, but prolonged exposure could result in significant liver fibrosis and even decompensated cirrhosis.¹⁰ Wendel-Garcia *et al.* studied critically ill COVID-19 patients receiving long-term ketamine infusions and found a dose-response relationship between ketamine and rising bilirubin and alkaline phosphatase levels, indicative of cholestatic liver injury. The minimum ketamine dose associated with hepa-

Table 1. Description of clinical ketamine-associated DILI cases with dosing and calculated RUCAM scores

Author	PubMed ID	Description	Dosing	Calculated RU-CAM Scores (*)
Wendel-Garcia <i>et al.</i> ¹²	35606831	This study found a significant dose-response relationship between the duration and dose of ketamine infusion and rising bilirubin levels, indicating cholestatic liver injury. Patients receiving ketamine had a multivariable adjusted competing risk hazard of developing cholestatic liver injury during their ICU stay of 3.2 (95% CI, 1.3–7.8; $p = 0.01$). The study concluded that long-term high-dose ketamine infusion is associated with an increased risk of cholestatic liver injury in critically ill COVID-19 patients and recommended avoiding high-dose ketamine for long-term sedation in these patients	Average of 1.4 mg/kg/h for a duration of nine days	8
Grewal <i>et al.</i> ¹⁴	33134030	This study reviewed the clinical, radiologic, and pathologic features of bile duct injury as a manifestation of DILI. It notes that bile duct injury due to DILI can lead to severe and chronic liver damage, including vanishing bile duct syndrome and sclerosing cholangitis-like changes	N/A	3*
Bartoli <i>et al.</i> ¹⁵	37547355	This study investigated the potential link between ketamine use and secondary sclerosing cholangitis in critically ill COVID-19 patients. The study explores whether the observed biliary injuries are due to the direct effects of SARS-CoV-2 on the biliary system or are associated with the use of ketamine in the ICU setting. This dose was associated with a significant increase in bilirubin levels and a higher risk of cholestatic liver injury in critically ill COVID-19 patients. The findings suggest a dose-response relationship between prolonged high-dose ketamine infusion and the development of cholangiopathies, highlighting the need for cautious use of ketamine in this patient population	1.4 mg/kg/h for a median duration of nine days	2*
Noppers <i>et al.</i> ⁷	21546160	Three cases of hepatotoxicity following repeated ketamine infusions for chronic pain management in CRPS type 1 patients were reported. The study found that all three patients developed significant elevations in liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase, and γ -glutamyl transferase) during the second infusion, indicating hepatotoxicity. The liver enzyme levels returned to normal within two months after the discontinuation of ketamine. This study highlights the potential hepatotoxicity of ketamine, particularly with prolonged and repeated infusions.	10–20 mg/h administered continuously over 100 h, with a second infusion occurring 16 days after the first	9
Yoo <i>et al.</i> ¹⁶	38505599	Presents a case of a 27-year-old female who developed hepatotoxicity following ketamine infusion for ICU sedation. The patient experienced a significant rise in LFTs, indicating possible ketamine-induced liver injury. The liver function normalized after the discontinuation of ketamine	0.5 mg/kg/h	9
Sharma <i>et al.</i> ¹⁷	38799518	The patient in the case report was administered ketamine intravenously for procedural sedation. Following the administration, the patient developed symptoms consistent with sphincter of Oddi dysfunction, including abdominal pain and elevated liver enzymes. The diagnosis was confirmed through sphincter of Oddi manometry, which showed elevated basal sphincter pressures.	0.5 mg/kg	9
Keta-Cov research group ¹⁸	33617925	This study investigates the relationship between prolonged ketamine infusion and the development of cholangiopathy in critically ill COVID-19 patients. The study included 243 patients with COVID-19-associated acute respiratory distress syndrome who received ketamine infusions. Ketamine was administered for a duration of nine days. The findings demonstrated a dose-response relationship between ketamine infusion and rising bilirubin levels, indicating a higher risk of cholestatic liver injury with prolonged ketamine use. The study concluded that high-dose ketamine should be avoided for long-term sedation in mechanically ventilated COVID-19 patients due to the increased risk of cholangiopathy.	1.4 [0.9–2.0] mg/kg/h	8

(continued)

Table 1. - (continued)

Author	PubMed ID	Description	Dosing	Calculated RU-CAM Scores (*)
Zhu <i>et al.</i> ¹⁹	32643900	Describes a case where a patient experienced significant liver enzyme elevation during ketamine infusion. The patient received ketamine for sedation. During the infusion, the patient developed markedly elevated liver enzymes, including alanine transaminase (ALT) and aspartate transaminase (AST), which were several times above the upper limit of normal. The liver enzyme levels returned to baseline after the discontinuation of the ketamine infusion.	0.5 mg/kg/h	9
Sear ²⁰	21555186	This case examines the hepatotoxic effects of ketamine when used for chronic pain management. The study involved patients receiving ketamine at doses ranging from 0.5 mg/kg/h to 1 mg/kg/h for prolonged periods. The findings indicated that chronic administration of ketamine at these doses led to significant elevations in liver enzymes.	0.5 mg/kg/h to 1 mg/kg/h	2*
Hewitt <i>et al.</i> ²¹	29135531	Describes a case where a patient with Complex Regional Pain Syndrome (CRPS) received subanesthetic ketamine infusions. The patient developed significant hepatobiliary complications, including biliary dilation, jaundice, and cholangitis, following repeated ketamine infusions.	0.5 mg/kg/h	9
Pappachan <i>et al.</i> ²²	24982568	This study examines the effects of chronic ketamine abuse on multiple organ systems. The study involved patients who had been abusing ketamine for an extended period. The findings highlighted significant multiorgan dysfunction, including hepatotoxicity, renal impairment, and neuropsychiatric disturbances. Patients exhibited elevated liver enzymes, indicative of liver injury, and some developed cholangiopathy, characterized by biliary dilation and jaundice. Renal complications included ketamine-induced cystitis and reduced renal function. Neuropsychiatric effects were also noted, including cognitive impairments and mood disturbances.	1-3 g daily	5*
Cotter <i>et al.</i> ⁶	34699023	This study analyzes 14 cases of hepatobiliary adverse events associated with repeated or continuous ketamine administration. The patients received ketamine for conditions such as complex regional pain syndrome or chronic pain. The doses varied, but the study highlighted adverse events, including liver enzyme elevation, biliary dilation, and cholangitis, occurring within four days of ketamine administration.	N/A	9
Kwan <i>et al.</i> ⁸	39818335	This study aimed to determine whether there is disproportionate reporting of hepatobiliary disorders in the US FDA Adverse Event Reporting System (FAERS) for individuals prescribed ketamine or esketamine. The study utilized a disproportionality analysis to evaluate the proportionality of reporting for various hepatobiliary disorders using the reporting odds ratio (ROR) and the lower limits of 95% confidence intervals of information components. Acetaminophen was used as a positive reference agent, and lithium as a neutral reference agent. For ketamine, there was disproportionately lower reporting of hepatitis, liver disorder, liver injury, drug-induced liver injury, hepatic failure, and acute hepatic failure compared to acetaminophen. Conversely, there was disproportionately higher reporting of hepatic function abnormalities and hepatic cytolysis for ketamine compared to acetaminophen.	N/A	2*
Seto <i>et al.</i> ¹⁰	29551711	This study investigates the effects of recreational ketamine use on the biliary system. The study included 257 Chinese individuals who had used ketamine recreationally at least twice per month for six months in the previous two years. The study found that 61.9% of the participants had biliary tract anomalies on MRCP. These anomalies were categorized into three patterns: diffuse extrahepatic dilation, fusiform extrahepatic dilation, and intrahepatic ductal changes without extrahepatic involvement. Elevated serum alkaline phosphatase (ALP) levels were significantly associated with these biliary anomalies. The study also noted that these cholangiographic anomalies were reversible after ketamine abstinence.	N/A	6

(continued)

Table 1. - (continued)

Author	PubMed ID	Description	Dosing	Calculated RU-CAM Scores (*)
De Tymowski <i>et al.</i> ²³	38304235	Examines the relationship between ketamine exposure, cholestatic liver injury, and outcomes in critically ill patients with severe burn injuries. This retrospective study analyzed patients across two periods: one with unrestricted ketamine prescription (ketamine-liberal) and another with capped ketamine dosage (ketamine-restricted).	Various	6
Wong <i>et al.</i> ¹¹	24534547	The study found a dose- and time-dependent relationship between ketamine exposure and cholestatic liver injury. Ketamine restriction was associated with a significantly reduced risk of cholestatic liver injury (adjusted odds ratio 0.16, 95% CI 0.04–0.50; $p = 0.003$). In the ketamine-restricted group, cholangitis was not observed, and there was a higher probability of three-month survival ($p = 0.035$).	Median 265 mg in the ketamine-liberal group. Median 20 mg in the ketamine-restricted group.	2*
Bell ²⁴	22436323	This study examines the potential toxic effects of ketamine when used for chronic noncancer pain management. The study highlights concerns about hepatotoxicity, neurotoxicity, and urinary tract toxicity associated with prolonged ketamine use. This dosing regimen was found to provide potent analgesia but also raised significant concerns about long-term safety, particularly regarding liver function and potential neurotoxic effects. The study underscores the importance of careful monitoring of liver enzymes and other potential adverse effects during ketamine therapy for chronic pain.	0.5 mg/kg/h administered intravenously over a period of four to fourteen days	2*

* Important co-existing medications or other causes of hepatitis were not excluded. DILI, Drug-induced liver injury; CI, confidence interval; CRPS, complex regional pain syndrome.

Table 2. Description of available ketamine-associated DILI (non-clinical) studies*

Author	PubMed ID	Description	Dosing
Lee <i>et al.</i> ⁹	19001360	This study observed the toxic effects of S-(+)-ketamine on human hepatoma HepG2 cells. The cells were exposed to S-(+)-ketamine at concentrations of 0.1, 0.5, 1, and 2 mM. The study found that S-(+)-ketamine induced significant apoptotic cell death in a dose-dependent manner. Key findings included increased release of lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (GPT), decreased cell viability, and significant DNA fragmentation. S-(+)-ketamine caused the translocation of Bax from the cytoplasm to mitochondria, decreased mitochondrial membrane potential, and reduced cellular ATP levels. This led to the release of cytochrome c into the cytoplasm and the activation of caspases-9, -3, and -6, which are key components of the apoptotic pathway. The study concluded that S-(+)-ketamine induces apoptosis in HepG2 cells through the Bax-mitochondria-caspase protease pathway, suggesting potential hepatotoxicity at clinically relevant or abused concentrations.	0.1, 0.5, 1, and 2 mM
Haller <i>et al.</i> ²⁵	38666919	This study investigated the hepatotoxic effects of various opioids and sedative drugs, including ketamine, on human liver cells. The study specifically examined the cytotoxicity and mechanisms of liver injury induced by these drugs. The results indicated that ketamine, at these concentrations, can cause significant hepatotoxicity, characterized by increased cell death and disruption of cellular functions. The study highlights the potential risks associated with the use of ketamine, particularly at higher doses, and underscores the importance of monitoring liver function during its clinical use.	Concentrations up to 100 μ M, incubated for two to three days
Bedir <i>et al.</i> ²⁶	34918884	This study investigated the hepatotoxic effects of ketamine and thiopental, both individually and in combination, on rat liver. The study evaluated various biochemical parameters to assess liver function and potential toxicity. The findings indicated that ketamine alone caused significant alterations in liver enzyme activities, suggesting hepatotoxicity. When combined with thiopental, the hepatotoxic effects were more pronounced, suggesting a potential synergistic effect between the two drugs.	50 mg/kg

(continued)

Table 2. - (continued)

Author	PubMed ID	Description	Dosing
Venâncio <i>et al.</i> ²⁷	23942268	This study investigated the long-term effects of chronic low-dose ketamine on liver mitochondrial function in rats. Adult rats were administered ketamine at doses of 5 mg/kg or 10 mg/kg twice a day for a fourteen-day period to mimic chronic treatments. The effects were evaluated ten days after the treatment ended. The study found that chronic ketamine administration led to a decrease in body weight gain during the treatment period, decreased hepatic glycogen content, and inhibited mitochondrial complex I and oxygen consumption when a glutamate-malate substrate was used. However, ketamine did not affect serum liver enzymes or oxidative stress parameters in liver mitochondria. These findings suggest that chronic ketamine use can lead to long-term mitochondrial bioenergetic deterioration in the liver.	5 mg/kg or 10 mg/kg for 14 days
Suliburk <i>et al.</i> ²⁸	15824646	This study investigated the impact of different anesthetics on liver injury induced by endotoxemia in rats. The study specifically examined the effects of ketamine and isoflurane on liver injury markers and inflammatory mediators. Ketamine was administered intraperitoneally. One hour after the administration of ketamine, the rats received lipopolysaccharide at a dose of 20 mg/kg to induce endotoxemia. The study found that ketamine significantly attenuated the increase in serum AST and ALT levels caused by LPS. Additionally, ketamine reduced hepatic inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) protein levels, as well as nuclear factor kappa B (NF-κB) binding activity. The study concluded that ketamine has hepatoprotective effects in the context of endotoxin-induced liver injury, likely mediated through the reduction of COX-2 and iNOS protein levels and modulation of NF-κB activity.	70 mg/kg
Chen <i>et al.</i> ²⁹	32108154	This study investigated the acute hepatic responses to a single administration of a ketamine/xylazine (K/X) mixture in rats. The dose of ketamine used in the study was 80 mg/kg, combined with 10 mg/kg of xylazine, administered intraperitoneally. The study utilized various imaging techniques, including dynamic contrast-enhanced MRI, nuclear magnetic resonance analysis, and fluorodeoxyglucose positron emission tomography, to assess liver function and structure. Key findings included a significant elevation of serum AST levels from 3–48 h post-injection, indicating liver injury. Additionally, obstructed sinusoidal circulation was observed for up to 36 h, and metabolic disturbances were detected as early as 3 h post-administration. Ultrasonography revealed increased lipid droplet accumulation in the liver from 1–16 h, which then declined.	80 mg/kg
Kalkan <i>et al.</i> ³⁰	23386779	This study investigated the impact of prolonged ketamine administration on liver function using histologic and biochemical methods. The study involved 30 male rats divided into a control group and four treatment groups. Ketamine was administered intraperitoneally at varying doses for two weeks. The results showed that histopathological changes in the liver were dose-dependent, with more severe and diverse changes observed in the groups receiving 80 and 100 mg/kg/day. These changes included significant ultrastructural alterations in mitochondria and the rough endoplasmic reticulum. The study concluded that prolonged ketamine administration causes hepatocellular toxicity and histological changes in a dose-dependent manner.	40, 60, 80, and 100 mg/kg twice a day for two weeks
Chan <i>et al.</i> ³¹	16076768	This study investigated the effects of ketamine on cytochrome P-450 (CYP) enzymes in the liver and its toxicological implications. Male Wistar rats were treated with ketamine at doses of 10, 20, 40, or 80 mg/kg intraperitoneally twice daily for four days. The study found that ketamine administration led to a dose-dependent increase in the activity of various CYP enzymes, including a 14-fold increase in pentoxyresorufin O-dealkylation activity at the highest dose (80 mg/kg). Additionally, ketamine induced the expression of multiple CYP isoforms, such as CYP1A, CYP2B, CYP2E1, and CYP3A. The induction of these enzymes was associated with increased susceptibility to hepatotoxicity, as evidenced by enhanced liver injury when rats were co-treated with carbon tetrachloride (CCl ₄) or cocaine. The conclusion suggests that ketamine can significantly alter hepatic enzyme activity, potentially leading to increased liver toxicity when combined with other hepatotoxic agents.	10, 20, 40, or 80 mg/kg
Wai <i>et al.</i> ¹³	22354085	This study investigated the effects of chronic ketamine use, both alone and in combination with alcohol, on liver and kidney function in mice. The study observed significant liver damage in the ketamine-treated mice, including fatty degeneration of liver cells, fibrosis, and increased levels of liver enzymes such as liver glutamic oxaloacetic transaminase, proliferative cell nuclear antigen, and lactate dehydrogenase after 16 weeks of treatment. The liver damage was more severe when ketamine was combined with alcohol, indicating a synergistic effect of the two substances.	30 mg/kg daily

*RUCAM scores were not calculated as these were non-clinical studies. DILI, drug-induced liver injury; CYP, cytochrome P-450.

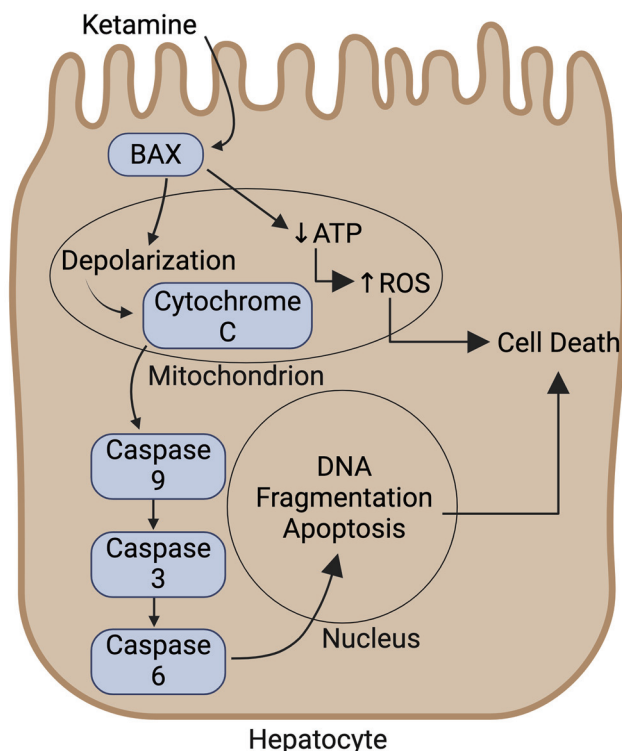


Fig. 1. A diagram depicting possible mechanisms of ketamine-induced hepatotoxicity, typically observed with prolonged recreational use. Upon exposure to ketamine, there is increased translocation of BAX, a pro-apoptotic protein, from the cytoplasm to the mitochondria, facilitating the release of cytochrome C. In the cytosol, cytochrome C binds to apoptotic protease activating factor-1, which activates caspase-9. Activated caspase-9 subsequently cleaves and activates downstream caspase-3 and caspase-6, leading to apoptosis through the formation of ROS and DNA fragmentation. Chronic ketamine exposure impairs mitochondrial complex I activity, resulting in decreased ATP production. Reduced ATP levels lead to increased ROS generation, causing damage to proteins, lipids, and DNA, and contributing to the activation of hepatic stellate cells. This process plays a critical role in hepatocyte injury and the subsequent development of liver fibrosis. ATP, adenosine triphosphate; BAX, Bcl-2-associated X protein; ROS, reactive oxygen species.

totoxicity was 1.4 mg/kg/h, leading the authors to caution against high-dose ketamine for long-term sedation in critically ill patients.¹² Additionally, Noppers *et al*. reported three cases of chronic recreational ketamine use resulting in obstructive jaundice and biliary tract abnormalities, including abnormal liver enzymes and biliary tract dilatation.⁷ Chronic exposure results in cumulative damage, affecting both the liver parenchyma and biliary system, whereas acute exposure is typically limited to transient hepatocellular injury.

Recreational vs. clinical use

As discussed previously, ketamine-induced liver injury has been documented in both recreational and clinical settings. Recreational users often consume higher doses and use ketamine more frequently, leading to a greater risk of liver injury with prolonged exposure. Additionally, recreational users may co-ingest other substances, such as alcohol, which can exacerbate liver damage. Studies have shown that long-term use can result in severe liver injury, including fibrosis and cirrhosis.^{11,13} In clinical settings, ketamine is administered in controlled doses with careful monitoring of liver function, reducing the risk of hepatotoxicity. For example, Cotter *et*

al. reported liver enzyme elevations in patients receiving repeated or continuous ketamine infusions for chronic pain, but these were managed through regular monitoring and dose adjustments.⁶ Clinical use typically involves shorter courses of treatment, limiting cumulative exposure and the potential for liver injury. Similarly, Noppers *et al*. reported cases of liver enzyme elevations during repeated ketamine treatments for chronic pain, with levels returning to normal upon drug discontinuation.⁷

Management

The primary treatment for ketamine-induced liver injury is discontinuation of ketamine use. This aligns with the general management of DILI, in which the offending agent should be promptly discontinued.³³ No specific pharmacologic treatment is currently recommended. Instead, supportive care remains the mainstay of management, which includes monitoring liver enzymes and liver function tests, as well as addressing symptoms.

Patients with ketamine abuse or addiction should also receive psychosocial support. One effective approach is the Crisis Accommodation Program, which integrates short-term hospitalization with community-based support. During hospitalization, patients undergo cognitive and psychosocial assessments, motivational interviewing, emotion management training, and lifestyle redesign interventions.³³

Conclusions

Although formal causality assessments of ketamine-induced hepatotoxicity are limited, several cases evaluated using RUCAM indicate a probable or highly probable association. Both medical and recreational ketamine use have increased dramatically over recent decades. The primary distinction between acute and chronic ketamine-induced hepatotoxicity lies in the duration and dose of exposure. Acute toxicity is rare but, when it occurs, it typically manifests as transient liver enzyme elevations—including alanine and aspartate aminotransferases, alkaline phosphatase, and γ -glutamyl transferase. Notably, no cases of acute liver failure due to ketamine exposure have been reported in the literature. Treatment includes immediate cessation of the drug and supportive care. Chronic toxicity, in contrast, results from prolonged recreational use, leading to more severe and potentially irreversible liver damage, including fibrosis, cholangiopathy, and cirrhosis. Patients receiving prolonged medically supervised ketamine treatment require close monitoring of liver enzymes, including AST, ALT, and ALP, as well as symptom evaluation. Treatment includes immediate discontinuation of ketamine, along with psychosocial support for those with addiction or dependence on recreational ketamine use.

Because ketamine is not widely recognized as a recreational drug, it may be overlooked as a cause of elevated liver enzymes. Therefore, in cases of acute or chronic hepatic damage where standard diagnostic approaches fail to identify a cause, ketamine hepatotoxicity should be considered.

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Conflict of interest

GYW has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013. The other author has no conflict of interests related to this publication.

Author contributions

BT conducted the literature review, synthesized the information, and authored the entirety of the commentary article. GYW served as the supervising mentor, providing guidance and critical revisions. Both authors have reviewed and approved the final manuscript.

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