British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(5): 53976
https://doi.org/10.31083/BJHM53976

Review

Beyond the High: A Narrative Review of the Chronic Complications of Recreational Ketamine Use

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Academic Editor: Deepak Singh-Ranger
Submitted: 5 September 2025 Revised: 7 December 2025 Accepted: 31 December 2025 Published: 18 May 2026

Abstract

Ketamine, initially developed as a dissociative anaesthetic, has seen expanding therapeutic applications, in managing treatment-resistant depression and chronic pain. However, its psychoactive properties have also been associated with a significant rise in recreational use globally. Chronic, high-dose recreational ketamine use is associated with dependence potential and a spectrum of long-term complications affecting multiple organ systems. This narrative review details the major chronic urological, neurological, neuropsychiatric and hepatobiliary complications that clinicians may encounter in individuals with long-term ketamine use, along with an overview of the potential risk of dependence. This review highlights the importance of heightened awareness among clinicians of the issues related to long-term ketamine use, enabling early identification and prompt, appropriate investigation and management.

Keywords: ketamine; substance-related disorders; urological diseases; gastrointestinal diseases; public health

1. Introduction

Ketamine is an arylcyclohexamine which is a synthetic derivative of phencyclidine that was first synthesised in 1962. It was approved for clinical use in the 1960s, and functions primarily as a dissociative anaesthetic [1]. Its primary mechanism of action involves non-competitive antagonism of the *N*-methyl-$_D$-aspartate (NMDA) receptor, a key component of glutamatergic neurotransmission involved in pain perception and neuroplasticity [2]. Furthermore, its influence on dopamine, opioid, and serotonin receptors contributes to its euphoric, analgesic, and hallucinogenic properties [3]. Clinically, ketamine has remained a valuable agent in anaesthesia, procedural sedation, and the management of chronic pain, due to its favourable profile of preserving airway reflexes and maintaining haemodynamic stability [4,5]. Since the mid-2000s, it has gained prominence in psychiatry for its rapid antidepressant effects in treatment-resistant depression [6], and is actively being investigated for other conditions such as post-traumatic stress disorder and alcohol dependence [7–9]. The rapid expansion of ketamine clinics, especially in the United States and Europe, offering off-label use of ketamine for conditions such as anxiety, depression, and post-traumatic stress disorder, has made ketamine increasingly accessible to the general population [8].

However, the same psychoactive properties that underpin its clinical benefits also drive its recreational use. At sub-anaesthetic doses, ketamine induces perceptual distortions, a sense of dissociation, and euphoria. At higher doses, it can lead to a profound dissociative state colloquially known as a "K-hole" [10]. Initially adopted within polydrug-using subcultures during the rave movements of the late 1990s [11], ketamine has since gained popularity across East and Southeast Asia, and more recently among young adults in the United Kingdom and the rest of Europe [12]. Its relative affordability, ease of administration, typically via insufflation, and rapid onset of action have facilitated its rising appeal in recreational settings [13].

While the acute psychoactive effects of ketamine are well established, growing evidence highlights that chronic, high-dose recreational ketamine use is associated with dependence potential and a spectrum of long-term complications affecting multiple organ systems, including urological damage, neurocognitive impairments, psychiatric disturbances, hepatobiliary and gastrointestinal dysfunction. Given the expanding therapeutic and recreational use of ketamine worldwide, a comprehensive understanding of its chronic complications is essential for developing effective management strategies and informing public health policies.

This narrative review uses selected peer-reviewed publications, to summarise the current knowledge on the long-term urological, neurological, neuropsychiatric, hepatobiliary and gastrointestinal complications associated with long-term ketamine use and discusses the understanding of the current approaches to the investigation and management of these complications.

2. Prevalence of Ketamine Use

Recreational ketamine use first emerged in the United States during the 1980s, often linked to underground rave culture. Throughout the 1990s, its use spread to Western

Europe, followed by a notable surge in East and Southeast Asia in the early 2000s [14]. In Hong Kong, ketamine rapidly became the drug of choice among adolescents, and by 2014, it was used by over 15% of all registered drug users in China, where it remains a prominent recreationally used substance, particularly in those under 21 years of age [15]. In England and Wales, the proportion of individuals aged 16–59 years reporting ketamine use doubled from 0.4% (117,000) in 2012 to 0.8% (269,000) in 2023. The increase has been even more marked among young adults aged 16–24 years, with reported use increasing from 0.8% in 2013 to 2.9% in 2024, whereas the use of other drugs has declined (cocaine falling from 6.2% to 3.8% and ecstasy from 4.7% to 2.2%) [16]. Across mainland Europe, the European Union Drugs Agency (EUDA) reported that ketamine accounted for 7% (2.9 tonnes) of all new psychoactive substances seized in 2023 [17]. Moreover, while ketamine levels in European city wastewater remained generally low in 2024, a significant proportion of monitored cities (14 out of 42) recorded a rise of at least 10% compared to the previous year, with the highest concentrations detected in cities in Belgium, the Netherlands, Hungary and Norway [17]. In the United States, although ketamine use is relatively less common, its popularity is growing. The National Survey on Drug Use and Health documented an 81.8% increase in usage between 2015 and 2019, with a further 40% rise from 2021 to 2022 [18]. In Australia, recent use among individuals aged 14 or older rose from 0.4% in 2016 to 1.4% in 2022–2023, with the highest prevalence among those aged 20–29 [19].

While ketamine is considered to have a wide safety margin with fewer fatalities compared to other recreational drugs [12], it can induce agitation, hallucinations, and psychosis, potentially leading to increased risk-taking behaviours. According to the Office for National Statistics in England and Wales in 2024, 60 deaths involving ketamine were recorded, compared with 1279 from cocaine and 2621 from opioids [16]. A 2023 systematic review on overdoses and deaths associated with ketamine and its analogues identified 123 fatalities involving ketamine, but it was the sole cause of death in only nine cases, with the majority linked to polysubstance use [20].

3. Dependence Potential of Long-Term Ketamine Use

Ketamine poses a substantial risk for abuse and dependence. The dependence potential of ketamine is linked to its stimulatory effects on dopaminergic and serotonergic pathways, with direct agonist activity at Dopamine 2 (D_2) and 5-Hydroxytryptamine 2A (5-HT2A) receptors contributing to its addictive properties [21]. Furthermore, ketamine dependence is associated with the interference of glutamate neurotransmission, which affects subcortical regions such as the nucleus accumbens, which is implicated in the neurobiology of addictive behaviours [22]. Preclinical studies in Sprague-Dawley rats have shown increased dopamine transmission in the limbic system associated with dependence development, as well as dose-dependent tolerance to ketamine's anaesthetic effects [23,24]. Human studies mirror these findings, with some individuals escalating their intake by as much as 600% to achieve desired effects [25]. This escalation is due to tachyphylaxis from repeated ketamine use, driven by the self-induction of multiple hepatic P450 enzymes, which accelerates the drug's clearance [26,27].

While ketamine dependence is not associated with classical physical withdrawal symptoms, chronic users have reported psychological disturbances such as anxiety, irritability, insomnia, and depressive symptoms following cessation [28]. Ketamine dependence can manifest with physical, psychological, and behavioural symptoms, including increased consumption, persistent desire to use, intense cravings, and tolerance. Reported withdrawal symptoms such as anxiety, sleep disturbances, and cognitive impairment have been linked to prefrontal and limbic dysfunction observed on magnetic resonance imaging (MRI) in chronic users. In contrast physical symptoms such as tremors or palpitations are less common compared to those associated with alcohol or opioid withdrawal [29].

In England, 12,418 young people accessed specialist substance misuse services in 2023, with those seeking treatment for ketamine use increasing from 1% in 2016 to 5.8% in 2023 [30], highlighting a growing public health burden. This trend is also reflected in Europe, with the number of clients receiving treatment for ketamine use increasing from 289 in 2018 to an estimated 1329 in 2023 [17].

Current treatment approaches for ketamine dependence largely rely on behavioural therapies, targeting the psychological dependence common among chronic users. There is currently a limited evidence base for pharmacological interventions in ketamine use disorder. A 2024 systematic review by Roberts *et al*. [31], composed primarily of case reports, found that benzodiazepines and haloperidol may be beneficial in the management of ketamine withdrawal. They reported that haloperidol appeared useful in stabilising psychotic symptoms. For relapse prevention and craving reduction, case-level evidence suggests potential roles for naltrexone, lamotrigine, and a combination of paliperidone palmitate with bupropion. However, it should be noted that most of these treatments are currently considered "off-label" and "unlicensed".

4. Chronic Urological Complications

Chronic ketamine use is strongly linked to severe urological complications, including ketamine-induced cystitis (KIC), colloquially referred to as 'ket-bladder'. First described in Canada in 2007, KIC was described in a case series of nine individuals who presented with lower urinary tract symptoms associated with recreational ketamine use [32]. In a large systematic review of 4314 patients with KIC, lower urinary tract symptoms such as frequency, urgency, nocturia, and suprapubic pain were the most re-

ported, with symptom severity strongly linked to the dose and duration of ketamine use [33]. A 2012 UK prevalence study reported that among individuals using ketamine in the past year, 26.6% experienced urinary symptoms, with 51% noting improvement upon cessation [34].

KIC is thought to arise from multiple interacting pathways. Ketamine and its metabolites exert direct toxic effects on the urothelium. Although only 2% of ketamine is excreted unchanged, 90% of metabolites (norketamine, dehydronorketamine, and conjugates of hydroxylated ketamine metabolites with glucuronic acid) are excreted renally, and these accumulate in the bladder, degrading tight junction proteins such as E-cadherin and claudins [35]. This damaged barrier triggers an immunoglobulin E (IgE)-mediated inflammatory response with infiltration of mast cells and eosinophils. Inflammatory enzymes, including nitric oxide synthase and cyclooxygenase-2, generate excessive nitric oxide and prostaglandins, promoting chronic inflammation and fibroblast activation, which leads to bladder wall fibrosis. Damaged urothelial cells also release adenosine triphosphate and antiproliferative factor, driving oxidative injury and further cell death [36]. Microvascular injury is thought to occur via NMDA receptor-mediated signalling and upregulation of inflammatory and angiogenic factors [37]. Over time, persistent inflammation leads to fibrosis of the bladder wall and diminished capacity, often resulting in detrusor overactivity and a contracted bladder [38]. Histological examination typically reveals ulceration, inflammatory infiltrates, and submucosal oedema [39].

In severe cases, upper urinary tract involvement can occur, with urethral strictures leading to hydronephrosis, vesicoureteral reflux, and renal papillary necrosis, collectively termed ‘ketamine-induced uropathy’ [40]. Among patients with KIC, approximately 20% develop urethral strictures, 8% show impaired renal function, and 30% present with hydronephrosis [33]. In ketamine-induced uropathy, the pathogenesis of direct urothelial damage is similar to KIC. Furthermore, lower urinary tract dysfunction, including reduced bladder compliance and vesicoureteral reflux, can contribute to secondary upper urinary tract damage. Chronic inflammation activates profibrotic pathways like transforming growth factor beta 1 (TGF-β1), contributing to fibrosis and ureteral strictures [41]. Damage to the upper urinary tract is typically progressive and asymptomatic.

KIC is typically classified into three stages. Stage 1 is marked by mild lower urinary tract symptoms with preserved bladder capacity. Stage 2 involves worsening symptoms, reduced bladder capacity and early upper urinary tract involvement. Stage 3 represents end-stage disease, with a contracted bladder and irreversible upper urinary tract damage. Renal imaging, urodynamic studies, and blood tests aid in the classification of ketamine uropathy [42].

Clinicians should actively clarify ketamine use in patients presenting with unexplained lower urinary tract symptoms and/or micro- or macroscopic haematuria as early recognition and cessation may result in early disease reversal [34]. The management of KIC is challenging, with absolute ketamine cessation being the cornerstone of treatment. Achieving this, however, often requires a multidisciplinary approach involving urologists, pain management specialists, and addiction treatment services. The British Association of Urological Surgeons 2024 consensus statement also advocated this multidisciplinary approach to KIC, emphasising immediate ketamine cessation alongside symptomatic relief with analgesia, anticholinergics, and/or β3-agonists, e.g., mirabegron [42]. For patients with Stage 1 and 2 disease, intravesical instillations containing lidocaine, hydrocortisone, and sodium hyaluronate, followed by intradetrusor botulinum toxin A, may be trialled. Li *et al.* [43] demonstrated superior outcomes with botulinum toxin A and hyaluronic acid compared to hydrodistension. Animal studies indicate hyaluronic acid promotes urothelial healing by reducing inflammation, enhancing barrier protein expression, and decreasing proinflammatory mediators [44]. For patients with end-stage bladder disease, surgical interventions like augmentation enterocystoplasty may be necessary, although these procedures carry significant risks and are typically reserved for those who have maintained abstinence for at least six months [45]. Upper urinary tract dysfunction in ketamine-induced uropathy requires regular monitoring, including renal and liver function tests every three months and renal imaging every six months. Temporising measures like ureteric stents or nephrostomy may be used for ongoing users, with definitive reconstructive surgery considered post-cessation [42].

Beyond cystitis and uropathy, chronic ketamine use has been associated with persistent haematuria, recurrent urinary tract infections and erectile dysfunction. The severity of erectile dysfunction often correlates with lower urinary tract symptom severity, suggesting a broader urogenital impact rather than an isolated side effect [46]. In a Taiwanese study of 1056 male ketamine users, 30.8% had erectile dysfunction, and 43% reported a significant negative impact on their sex lives due to lower urinary tract symptoms [47].

Chronic ketamine use can cause progressive lower and upper urinary tract damage, including cystitis, urethral strictures, and renal impairment, with severity closely linked to dose and duration. Early recognition and cessation are critical, as timely intervention can reverse symptoms and prevent long-term complications.

5. Chronic Neurological and Neuropsychiatric Complications

Chronic recreational ketamine use is increasingly recognised as a cause of diverse neurological complications, including cognitive impairment, psychiatric symptoms, and structural brain changes. While ketamine is therapeutically employed for its rapid antidepressant effects at subanaesthetic doses, chronic misuse disrupts neuroplastic and neurotransmitter pathways, leading to adverse func-

tional and structural changes [48]. Evidence regarding ketamine's neurotoxicity is mixed. In controlled, short-term, or low-dose contexts, such as in traumatic brain injury and stroke, ketamine may be neuroprotective by reducing excitotoxic injury and promoting synaptic resilience [49]. Mechanistically, transient NMDA receptor antagonism enhances glutamatergic pathways, brain-derived neurotrophic factor, and mammalian target of rapamycin (mTOR) signalling, promoting synaptogenesis [50]. Glutamate, the brain's primary excitatory neurotransmitter, is crucial for synaptic plasticity, learning, and memory [51]. Preclinical studies further suggest NMDA antagonists may modulate neurodegenerative processes through proteasome activation and synaptic protein remodelling in diseases like Alzheimer's and Parkinson's [52].

In contrast, chronic or high-dose exposure leads to neurotoxic and neurodegenerative effects. Persistent NMDA receptor blockade disrupts glutamatergic balance, causing excitotoxicity, oxidative stress, and neuronal apoptosis [53,54]. Structural MRI imaging consistently demonstrates grey matter reductions in frontal and limbic regions critical for executive function and emotional regulation. Affected regions include the medial and dorsolateral prefrontal cortices, orbitofrontal cortex, insula, and precuneus [55–57]. Adolescent-onset users may exhibit vulnerability, with one study noting reduced left precuneus volume compared to adult-onset users [57]. Conversely, one study reported increased grey matter volume in the left caudate nucleus, suggesting complex, region-specific effects [58].

Diffusion-weighted MRI studies of white matter integrity showed varied findings. Some studies using fractional anisotropy reported reductions in fractional anisotropy in frontal and temporoparietal white matter tracts [59] and altered connectivity between the caudate and prefrontal cortex has been linked to dissociative symptoms [60]. Conversely, Liang *et al*. [61] found increased white matter volume and enlarged caudate nuclei, possibly indicating compensatory hypertrophy or neuroinflammation. A longitudinal study found progressive white matter lesions emerging within a year of use, followed by cortical atrophy after four years, with severity correlating with duration and dose [62]. Functionally, these brain changes manifest as impairments in verbal fluency, executive function, spatial working memory, and verbal learning, the latter showing a strong correlation with lifetime ketamine exposure [54,63,64]. Functional MRI studies using regional homogeneity analysis have shown decreased synchrony in the anterior cingulate cortex, a region involved in decision making, attention and emotion regulation [65]. Chronic animal exposure models have shown tau hyperphosphorylation, neuronal apoptosis, and cerebellar degeneration, features suggestive of Alzheimer-like pathology [66,67].

The relationship between ketamine use and psychiatric conditions is complex. While ketamine produces rapid antidepressant effects in clinical settings, particularly for treatment-resistant depression, long-term recreational use is linked to increased rates of depression, anxiety, suicidality, and substance-induced psychosis [68–70]. A Hong Kong study found that among treatment-seeking ketamine-dependent individuals, 31.8% experienced substance-induced psychosis and 27.9% were diagnosed with depressive disorders [70]. Both frequent and abstinent users have shown elevated depressive symptoms over time [71]. These findings may relate to ketamine-induced disruption of functional connectivity in brain regions involved in mood regulation, such as the subgenual anterior cingulate cortex, orbitofrontal cortex, and ventromedial prefrontal cortices [72]. In frequent users, depressive symptoms may reflect both the neurobiological effects of chronic use and the psychological burden of dependence, mirroring patterns seen in opioid and alcohol misuse [73]. In abstinent former ketamine users, symptoms are less well understood but may result from lifestyle changes and loss of drug-related coping mechanisms.

Ketamine can also induce schizophrenia-like symptoms including paranoia, hallucinations, and anhedonia, particularly with subanaesthetic doses [74]. Frequent long-term use is associated with higher levels of delusional ideation, and dissociative symptoms [69]. These effects may be related to disrupted glutamatergic and dopaminergic signalling in the prefrontal cortex and hippocampus, pathways also implicated in schizophrenia [75,76]. Positron emission tomography (PET) imaging has shown upregulation of Dopamine 1 (D_1) receptors in the dorsolateral prefrontal cortices of chronic users, like findings in schizophrenia [77,78]. This could be a compensatory response to altered prefrontal dopamine function or related to neuroinflammation [68,79].

Beyond cognitive and psychiatric symptoms, chronic users may develop overt neurological deficits. A case report documented a 28-year-old male who died following an eight-year history of daily ketamine inhalation, during which he developed progressive lower limb weakness and recurrent seizures. Imaging revealed severe cerebral atrophy and enlarged ventricles [80]. Another case study described a woman who developed amnesia and dissociative immobility after escalating ketamine use [81]. The mechanisms of neurotoxicity are thought to involve direct neurotransmitter toxicity, apoptosis, and potentially neurogenic vasodilation leading to reduced brainstem blood supply [82].

Prenatal ketamine exposure poses significant neurodevelopmental risks. Preclinical studies show that in utero exposure induces neurotoxicity through NMDA receptor overexpression, mitochondrial dysfunction, and impaired neurogenesis [83], leading to anxiety-like behaviours in adult offspring in animal models [84]. Limited human data includes a case report of intrauterine growth restriction and neonatal electroencephalography (EEG) abnormalities following confirmed prenatal ketamine exposure, highlighting teratogenic concerns [85].

Currently, management of ketamine-induced neurotoxicity relies on early identification and cessation of use. In a longitudinal study of dependent users, 12 weeks of abstinence was associated with partial cognitive recovery, and improvements in mood and anxiety symptoms [86]. Pharmacologically, antioxidants such as *N*-acetyl cysteine and omega-3 fatty acids have shown promising neuroprotective effects in models, although currently there is no evidence for their use in humans [87,88].

In summary, chronic recreational ketamine use is associated with cognitive impairment, and psychiatric symptoms. While low-dose, short-term use may confer neuroprotective benefits, chronic or high-dose exposure results in excitotoxicity, neurodegeneration, and schizophrenia-like symptoms, highlighting ketamine's paradoxical potential for both neuroprotection and neurotoxicity.

6. Hepatobiliary and Gastrointestinal Complications of Chronic Ketamine Use

Ketamine misuse is an emerging cause of significant hepatobiliary and gastrointestinal (GI) pathology. While acute use can cause transient hepatotoxicity, chronic exposure is linked to more severe and potentially irreversible hepatic and biliary damage. GI complaints, including epigastric pain and gastritis, are also common among long-term users.

6.1 Hepatobiliary Complications

Acute ketamine-induced hepatotoxicity typically presents with nonspecific symptoms like fatigue, anorexia, and right upper quadrant pain, often with transient elevations in liver enzymes (alanine aminotransferase and aspartate aminotransferase) that normalise upon drug cessation [89]. Current evidence suggests acute exposure causes primarily hepatocellular injury, while chronic use leads to cholestatic injury associated with hepatobiliary dysfunction, including cholestasis and biliary tract abnormalities resembling sclerosing cholangitis [90]. Ketamine-induced cholangiopathy was first reported by Wong *et al*. [91] in a case series of three patients presenting with features resembling secondary sclerosing cholangitis in Hong Kong. A more recent systematic review by Teymouri *et al*. [92] analysed 17 such cases and identified typical clinical features including epigastric and/or right upper quadrant pain, nausea, vomiting, and less commonly, jaundice and fever. Imaging often revealed fusiform dilation of the common bile duct (CBD) without obstruction [93]. In a cross-sectional study of 297 ketamine users, 9.8% demonstrated biochemical cholestasis. In a subset of these patients, liver biopsy revealed bridging fibrosis, and Magnetic Resonance Cholangiopancreatography (MRCP) findings included CBD dilation [94].

The mechanisms underlying hepatobiliary injury remain unclear, though several hypotheses have been proposed. *In vitro* studies have demonstrated that chronic ketamine exposure promotes BCL2-associated X protein (BAX)-mediated mitochondrial release of cytochrome c, activating caspases and inducing apoptosis via reactive oxygen species and DNA fragmentation, alongside impaired mitochondrial adenosine triphosphate (ATP) production [95]. This cascade contributes to hepatic stellate cell activation and the development of liver fibrosis [90].

Biliary injury relates to ketamine metabolism and excretion; while 90% of metabolites are excreted renally, the remaining 10% pass via the biliary route [27,96]. These metabolites may exert direct cytotoxic effects on cholangiocytes. Additionally, ketamine's NMDA receptor antagonism or potential muscarinic agonism may dysregulate the sphincter of Oddi, resulting in biliary spasm, bile stasis, and CBD dilation [97,98]. Bile stasis may promote precipitation of norketamine, potentially causing obstruction and inflammation of the biliary tree [98].

The mainstay of treatment for ketamine-induced cholangiopathy is cessation of ketamine use, which typically leads to gradual improvement in liver function tests and resolution of biliary abnormalities over several months [91,92,99,100]. In selected cases, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy or biliary stenting has been utilised despite the absence of radiologically confirmed strictures. These interventions have been associated with a reduction in CBD calibre on follow-up imaging and improved liver function, suggesting a potential role in alleviating functional obstruction or bile stasis [91,92].

The European Association for the Study of the Liver (EASL) recommends a structured approach for any suspected drug-induced cholestasis, including imaging, serological testing and biopsy where needed [101]. Pharmacological treatments such as ursodeoxycholic acid may be considered selectively. Corticosteroids have shown minimal benefit in drug induced liver injury and are typically reserved as a last resort [102]. No guidelines currently exist to inform management of persistent cholangiopathy post ketamine cessation, and ongoing dysfunction warrants hepatology referral. Although outcomes are generally favourable following cessation, severe cases may still progress to liver failure and require transplantation despite abstinence [97,103].

6.2 Gastrointestinal Complications

Chronic ketamine use has been associated with a spectrum of gastrointestinal complications, including gastritis, peptic ulceration, and a distinctive syndrome of recurrent, severe upper abdominal pain commonly referred to as "K-cramps" [14]. This typically presents as cramping epigastric pain, often with nausea or vomiting [10]. A Spanish online survey reported 'frequent' abdominal pain in 27% of users [104], while a 10-year review of emergency attendances in Italy found abdominal pain in 15% and vomiting in 10.8% of cases [105]. In a study of 615 ketamine users in Hong Kong, 168 reported upper GI symptoms, predominantly epigastric pain (98%), vomiting (29%) and melaena

(10%). Endoscopy showed gastritis in 50%, with *Helicobacter pylori* infection in 20%, suggesting a multifactorial aetiology [106].

The pathophysiology of K-cramps is speculative, and the variation in symptoms suggests a clinical syndrome reflecting possible dysfunction across multiple abdominal organs, rather than a single entity. NMDA receptor blockade in GI smooth muscle may impair motility and promote visceral hypersensitivity [107]. Microvascular injury, recognised in ketamine induced uropathy, might cause similar ischaemia and inflammation in the upper GI tract [108]. Additional mechanisms include mucosal cytotoxicity, immune-mediated inflammation, or referred pain from biliary pathology [108,109].

Following appropriate clinical and radiological evaluation to exclude alternative causes, the primary evidence-based treatment for K-cramps, as with other chronic ketamine related issues, is stopping ketamine use. In a retrospective study by Poon *et al*. [110], abstinence was associated with a 12.5-fold increase in the likelihood of symptom resolution compared to continued use. Case reports support this observation, documenting symptomatic improvement within 24 hours of discontinuation and recurrence upon relapse [111]. Pharmacological treatments have not demonstrated consistent efficacy, though antispasmodics and simple analgesics are sometimes used anecdotally.

7. Future Research and Public Health Priorities

Currently, management of ketamine related long-term complications focuses on cessation of ketamine use and symptomatic treatment of those complications. The evidence base for which symptomatic treatment is effective is limited and needs to be strengthened. As our understanding of the mechanisms underlying chronic ketamine-related harm develops, there is a need for research that looks to modify or reverse developing or established complications.

Future work should progress along three linked areas. First, in dependence and withdrawal, appropriate clinical trials are required to evaluate the safety and effectiveness of agents currently used in acute withdrawal management such as benzodiazepines and haloperidol. In addition, there is work needed to understand whether there is a role for drugs such as naltrexone, lamotrigine, paliperidone and/or bupropion in preventing relapse after cessation of use. Second, information from current preclinical studies, such as the neuroprotective effects of acetylcysteine and omega-3 supplements, should be translated into clinical trials to determine whether ketamine-related cognitive impairment can be attenuated or prevented. Third, research into peripheral organ complications should prioritise mechanism-directed therapies, including anti-fibrotic approaches for ketamine-induced cystitis and interventions for sclerosing cholangiopathy.

Alongside clinical research, co-ordinated public health strategies are required to monitor patterns of ketamine use, improve early identification in primary and emergency care, and ensure access to harm reduction advice and specialist support services. Together, these efforts are essential to shift management from reactive supportive care of ketamine related long-term issues towards proactive, evidence-based prevention and targeted effective treatment of health complications from long-term ketamine use.

8. Conclusion

Data from a variety of sources show that increasing long-term use of ketamine is becoming a significant global concern. This is associated not only with dependence, but also a range of urological, neurological, neuropsychiatric, hepatobiliary and gastrointestinal complications. Although these complications have been described previously, the rising prevalence of ketamine use is resulting in a growing burden of ketamine-related morbidity and healthcare utilisation. Hospital physicians across all specialties should be aware of these issues to facilitate the early recognition and diagnosis of them, promote cessation of ketamine use, and initiate appropriate multidisciplinary investigation and management. To facilitate this, clinicians should be prompted to enquire routinely about ketamine use, particularly in younger patients presenting with unexplained urological, hepatobiliary, or neurological symptoms. Public health initiatives and further research into effective treatments for these chronic complications are urgently needed.

Key Points

• This review highlights the growing global concern of chronic recreational ketamine use, which carries significant risks beyond its acute psychoactive effects.

• Long-term, high-dose use is strongly associated with dependence and a wide spectrum of complications affecting the urological, neurological, psychiatric, hepatobiliary, and gastrointestinal systems.

• Ketamine-induced cystitis and uropathy are among the most debilitating complications, leading to irreversible bladder and renal damage.

• Hepatobiliary dysfunction, including ketamine-induced cholangiopathy, alongside gastrointestinal syndromes such as “K-cramps”, further underscores the multisystem toxicity of the drug.

• Early recognition, cessation, and multidisciplinary management are critical, while public health measures and further research remain urgently needed.

Availability of Data and Materials

Not applicable.

Author Contributions

KLE, PID, and DMW developed the concept for the review. KLE undertook the initial literature review and drafted the manuscript. PID and DMW validated the literature review. All authors contributed to revising the

manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

KLE declares no conflicts of interest. DMW is the Chair of the UK Advisory Council on the Misuse of Drugs, Expert Advisor to the European Union Drugs Agency, United Nations Office on Drugs and Crime and the World Health Organization, Vice Chair of the Scientific Committee of the European Association of Poisons Centres and Clinical Toxicologists, a member of the Board of Trustees of the American Academy of Clinical Toxicology and an editorial board member of the Journal of Medical Toxicology and the British Journal of Clinical Pharmacology; this article is written independently of these activities. PID is a Commissioner to the UK Commission on Human Medicines and the President of the European Association of Poisons Centres and Clinical Toxicologists; he is an Expert Adviser to the UK Advisory Council on the Misuse of Drugs, the European Union Drugs Agency, the United Nations Office on Drugs and Crime, and the World Health Organization; he is a member of the International Board of the British Journal of Clinical Pharmacology and associate editor of Clinical Toxicology. This article was written independently of these roles.

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