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REVIEW / DERLEME

The Dark Side of Ketamine: Brain, Bladder, and Beyond: a Focused Clinical Review for Emergency Medicine Clinicians

Ketaminin Karanlık Yüzü: Beyin, Mesane ve Ötesi: Acil Tıp Klinisyenleri İçin Odaklanmış Bir Klinik Derleme

Sergey Motov[1]

ABSTRACT

Ketamine is an indispensable therapeutic in emergency medicine, yet its pharmacologic profile carries a unique constellation of adverse effects that emergency medicine clinicians must recognize and manage. This focused clinical review examines four categories of these ketamine-specific adverse effects encountered in the emergency department (ED): acute psycho-perceptual adverse effects (PPAEs) (during analgesic use), ketamine-induced cystitis (KIC) (a progressive uropathy), ketamine-associated cholangiopathy (a sclerosing cholangitis–like syndrome), and ketamine use disorder (KUD) (encompassing dependence and withdrawal). The review summarizes current evidence addressing epidemiology, pathophysiology, clinical presentation, ED management, and disposition of patients experiencing these adverse effects and provides a practical approach for their management. Recreational ketamine use has surged globally, with illicit seizures in the United States increasing over 1,100% between 2017 and 2022 and UK treatment admissions rising fivefold since 2015. Psycho-perceptual effects occur in up to 92% of patients receiving sub-dissociative ketamine by intravenous push but can be reduced by approximately 40% with slow infusion. Ketamine-induced cystitis affects 25–27% of chronic users and is progressive yet partially reversible with early cessation. Ketamine-induced cholangiopathy occurs in roughly 10% of chronic users and mimics primary sclerosing cholangitis. Across all chronic toxicity syndromes, ketamine cessation is the single most important intervention. Emergency physicians are uniquely positioned to identify these conditions, initiate treatment, and connect patients to specialized care.

Keywords: Ketamine, analgesia, substance-related disorders, drug-related side effects and adverse reactions, emergency service

ÖZ

Ketamin, acil tıpta vazgeçilmez bir terapötik ajan olmakla birlikte, farmakolojik profili acil tıp klinisyenlerinin tanıması ve yönetmesi gereken özgün bir advers etki kümesi taşır. Bu odaklanmış klinik derleme, acil serviste karşılaşılan ketamine özgü advers etkilerin dört kategorisini incelemektedir: akut psiko-algısal advers etkiler, analjezik kullanım sırasında, ketamin ilişkili sistit, progresif bir üropati, ketamin ilişkili kolanjiyopati, sklerozan kolanjit benzeri bir sendrom, ve ketamin kullanım bozukluğu, bağımlılık ve yoksunluğu kapsayacak şekilde. Derleme, bu advers etkileri yaşayan hastalarda epidemiyoloji, patofizyoloji, klinik prezentasyon, acil servis yönetimi ve taburculuk ya da sevk kararlarına ilişkin güncel kanıtları özetlemekte ve yönetimleri için pratik bir yaklaşım sunmaktadır. Rekreasyonel ketamin kullanımı küresel olarak belirgin şekilde artmıştır. Amerika Birleşik Devletleri'nde yasa dışı ketamin ele geçirme vakaları 2017 ile 2022 arasında %1.100'ün üzerinde artmış, Birleşik Krallık'ta ise tedavi başvuruları 2015'ten bu yana beş katına çıkmıştır. Psiko-algısal etkiler, intravenöz hızlı enjeksiyon yoluyla subdissosiyatif ketamin alan hastaların %92'sine kadarında görülebilmekte, ancak yavaş infüzyon ile yaklaşık %40 oranında azaltılabilmektedir. Ketamin ilişkili sistit, kronik kullanıcıların %25 ila %27'sini etkilemekte olup progresiftir, ancak erken dönemde ketaminin bırakılmasıyla kısmen geri döndürülebilir. Ketamin ilişkili kolanjiyopati, kronik kullanıcıların yaklaşık %10'unda ortaya çıkmakta ve primer sklerozan kolanjiti taklit etmektedir. Tüm kronik toksisite sendromlarında ketaminin bırakılması en önemli tek müdahaledir. Acil tıp hekimleri, bu durumları tanımlamak, tedaviyi başlatmak ve hastaları uzmanlaşmış bakıma yönlendirmek açısından benzersiz bir konumdadır.

Anahtar Kelimeler: Ketamin, analjezi, madde ilişkili bozukluklar, ilaca bağlı yan etkiler ve advers reaksiyonlar, acil servis

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[1]Maimonides Medical Center, Department of Emergency Medicine, Brooklyn, NY, USA.

Corresponding Author: Sergey Motov, Professor of Emergency Medicine. **Address:** Maimonides Medical Center, Department of Emergency Medicine, 4802 Tenth Avenue, Brooklyn, NY 11219. **Telephone:** ++ 1-6463209161. **e-mail**: smotov@maimo.org.

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Introduction

Ketamine is a phencyclidine derivative that received FDA approval in 1970 that primarily acts as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (1). Its clinical profile—dissociative anesthesia, potent analgesia, sympathomimetic hemodynamic support, and preservation of respiratory drive—has made it an indispensable therapy in emergency practice (2-4). Sub-dissociative dose ketamine (SDK, typically 0.1–0.3 mg/kg IV) has gained broad adoption for acute pain management in the emergency department (ED), while full dissociative doses (1–2 mg/kg IV) remain the standard for procedural sedation (4,5).

Beyond these established uses, ketamine has attracted renewed interest as a rapid-acting antidepressant. The FDA's approval of intranasal esketamine for treatment-resistant depression has considerably widened its clinical footprint (6). At the same time, recreational ketamine use has surged globally. In the United States, the total weight of illicit ketamine seized climbed by over 1,100% between 2017 and 2022 (7,8). In the United Kingdom, self-reported use has more than doubled since 2016, with a threefold rise among people under 25, and the number of adults entering treatment for ketamine use disorder (KUD) has risen fivefold since 2015 (8,9). This dual trajectory—expanding medical indications on one hand and escalating recreational misuse on the other—has exposed a spectrum of ketamine-related harms that go well beyond its analgesic, sedative, and dissociative effects (2,10). This review addresses the four most clinically significant adverse-effect categories through an evidence-based and clinically focused framework designed for emergency clinicians.

Psycho-Perceptual Adverse Effects

Epidemiology and Pathophysiology

Psycho-perceptual adverse effects (PPAEs)—feelings of unreality, dizziness, mood changes, and vivid imagery—are the most common side effects of ketamine analgesia in the ED (2,4,11). Prospective data show that PPAEs occur in up to 92% of patients receiving SDK by rapid intravenous push, making them a near-universal phenomenon at standard analgesic doses delivered quickly (4,5).

The underlying mechanism for PPAEs centers on ketamine's blockade of NMDA receptors on GABAergic interneurons, which triggers glutamatergic disinhibition and enhanced excitatory transmission across thalamocortical circuits (2,12). This disruption of thalamocortical gating functionally disconnects sensory input from cortical processing, producing the characteristic dissociative state. Ketamine also amplifies dopaminergic and serotonergic activity in the prefrontal cortex, further altering perception and mood (12,13). These effects are both dose-dependent and rate-dependent: a rapid bolus generates higher peak plasma concentrations and considerably more perceptual disturbance than the same dose infused slowly (5,13). The clinical spectrum ranges from mild perceptual distortion to a distressing "out-of-body" experience. Common manifestations include a sense of floating, visual hallucinations, altered time perception, nystagmus, and feelings of unreality (2,12,13). Although self-limiting—typically resolving within 15 to 45 minutes—these effects can be profoundly unsettling for unprepared patients and may provoke combativeness, treatment refusal, or a perceived iatrogenic crisis (2,12,13).

ED Prevention, Management, and Disposition

Commonly utilized strategies include pre-administration coaching, slow infusion (15–30 minutes rather than push), lower initial dosing (0.1–0.15 mg/kg), and, in rare instances, premedication with midazolam 0.5–1 mg IV or haloperidol 2.5 mg IV for severely anxious patients (5,13) (Table 1). Randomized clinical trials on sub-dissociative IV ketamine analgesia in ED patients with acute painful conditions demonstrated a reduction of feelings of unreality by approximately 40% (92% with push vs. 54% with infusion) while preserving analgesia (4,5). When PPAEs develop despite preventive measures, verbal reassurance and guidance should be employed first; consideration should then be given to slowing or terminating (in extreme cases) the infusion and administering low-dose midazolam or haloperidol (13,14). Patients may be discharged once the PPAEs are resolved and patients are back to their baseline. It is important to tell the patient and to document in the chart the patient's PPAE experience as an expected pharmacologic effect of ketamine and not an allergic reaction.

Ketamine-Induced Cystitis

Epidemiology

Ketamine-induced cystitis (KIC) was first reported in 2007 by Shahani and colleagues, who described nine chronic recreational users presenting with severe lower urinary tract symptoms (LUTS) including dysuria, frequency, urgency, nocturia, pelvic pain, and gross hematuria [15]. Since then, its prevalence has risen in parallel with increasing

Strategy	Details	Evidence
Pre-administration coaching	Set expectations; normalize transient perceptual changes; reassure patient	Consensus recommendation: reduces distress and improves tolerability (4,5)
Slow infusion (15–30 min)	Replace IV push with short infusion at 0.3 mg/kg over 15 min	RCTs: ~40% reduction in unreality (IVP 92% vs SI 54%); preserved analgesia (4,5)
Lower initial dose	0.1–0.15 mg/kg IV instead of 0.3 mg/kg	Reduces peak plasma levels and PPAE severity (3,4)
Premedication	Midazolam 0.5–1 mg IV or haloperidol 2.5 mg IV	Reduces recovery agitation in procedural sedation (14); reserve for severely anxious patients

Table 1. Strategies for prevention of ketamine psycho-perceptual adverse effects
IV: Intravenous, IVP: Intravenous push, PPAE: Psycho-perceptual adverse effect, RCTs: Randomized controlled trials, SI: Slow infusion.

recreational use (16). Approximately 25–27% of chronic ketamine users develop ketamine-induced uropathy of different degrees (17). A large survey of 1,285 recent ketamine users found that more than a quarter of surveyed participants reported urinary symptoms, with higher doses and more frequent use associated with significantly greater symptom burden (18). A 2025 cross-sectional study of 274 individuals with self-identified ketamine use disorder (KUD) found that 60% reported bladder problems and 56% had abdominal cramping ("K-cramps"); treatment-seeking users consumed significantly more ketamine daily (mean 2.67 g vs. 1.68 g) (8). Notably, 73% of participants identified ketamine as their primary drug of use, emphasizing that this is not merely an incidental finding in polysubstance users (8).

Pathophysiology

Ketamine and its metabolite norketamine are excreted via the urinary tract, where they exert direct toxic effects on the urothelium: epithelial denudation, tight-junction destruction, and barrier breakdown (17,19). Once the urothelial barrier fails, urine containing irritative substances penetrates the submucosal and muscular layers, triggering a cascade of inflammation and progressive fibrosis. Histopathology shows a distinctive pattern of eosinophilic and mast cell infiltration extending through the mucosa, submucosa, and muscle layers, accompanied by submucosal fibrosis, muscle hypertrophy, and collagen deposition—features that distinguish KIC from both interstitial cystitis/painful bladder syndrome and bacterial cystitis (17,19,20). In advanced disease, the inflammatory process extends beyond the bladder to involve the ureters, producing dilation, wall thickening, vesicoureteral reflux, and hydronephrosis (19-21). Disease progression follows three broadly recognized phases: an early inflammatory stage that is largely reversible, an intermediate fibrotic stage with thickened bladder walls and diminishing capacity, and a late contracture stage with transmural fibrosis and upper tract compromise (Table 2) (20).

ED Management and Disposition

Emergency physicians should suspect KIC in any adult presenting with recurrent LUTS that have not responded to empiric antibiotics and/or analgesics and should specifically query ketamine use, as patients rarely volunteer this information on their own (8,17). The diagnostic workup includes urinalysis (typically demonstrating sterile pyuria and hematuria), urine culture (negative), a basic metabolic panel to assess renal function, and point-of-care ultrasound or formal imaging to evaluate for hydronephrosis, bladder wall thickening, and reduced bladder capacity (17,19). Cystoscopy, while not performed in the ED, remains the definitive diagnostic study and characteristically reveals a contracted, inflamed bladder with ulcerative mucosal changes (19).

From a treatment perspective, ketamine cessation is the single most important intervention and the cornerstone of every treatment plan: symptoms improve in roughly 51% of users with cessation alone (18), and early cessation helps prevent progression to upper urinary tract involvement (17,19). However, abrupt cessation poses its challenges as patients often experience withdrawal symptoms and frequent relapses and may even increase their ketamine consumption in an attempt to self-medicate their worsening urinary pain (21). A practical alternative is to recommend a supervised taper over days to weeks, ideally in collaboration with an addiction specialist, to ease the psychological withdrawal burden (21,22).

First-line pharmacotherapy in the ED includes NSAIDs (ibuprofen 400 mg every 6–8 hours or ketorolac 15 mg IV every 6 hours), anticholinergic medications (oxybutynin 5 mg three times daily), a short steroid course (prednisone 50 mg daily for 7 days), and pentosan polysulfate (100 mg three times daily)—the only FDA-approved agent for interstitial cystitis, which has also demonstrated efficacy in KIC (Table 3) (17,19,22). Outside the scope of ED care, intravesical hyaluronic acid instillation and botulinum toxin A injection are reserved for pharmacologic-resistant cases, while surgical interventions including augmentation cystoplasty and cystectomy with ileal conduit may be necessary in end-stage disease (17,19,22). At discharge, counseling about ketamine cessation, provision of analgesia, and referral to both urology and addiction medicine are essential to successful management of KIC. Admission is warranted for patients with urinary retention, severe uncontrolled pain, or obstructive uropathy with renal impairment.

Ketamine-Associated Cholangiopathy

Epidemiology

Ketamine-associated cholangiopathy (KAC) affects approximately 10% of chronic users, and all reported cases follow a cholestatic pattern of liver injury (23). This condition typically develops after three or more years of regular use (23), though cases have also been reported in the setting of prolonged medical ketamine infusions for sedation in the ICU (24). A critically important diagnostic clue is that roughly 75% of affected patients also have concurrent ketamine-induced cystitis (25,26). A clear dose-effect and duration-effect relationship exists, with prolonged high-dose exposure correlating with rising bilirubin levels and increasing risk of cholestatic injury (24).

Phase	Underlying changes	Symptoms	Management
Early (inflammatory)	Urothelial inflammation/edema; detrusor preserved	Frequency, urgency, dysuria; mild capacity reduction	Cessation; NSAIDs; anticholinergics; steroids; opioids (in severe cases); pentosan polysulfate
Intermediate (fibrotic)	Submucosal fibrosis; wall thickening; capacity loss	Escalating LUTS; suprapubic pain; reduced voided volumes	Intravesical hyaluronic acid or botulinum toxin A instillation; hydrodistension
Late (contracture)	Transmural fibrosis; bladder contracture; upper tract dilation	Severe pain; minimal capacity; hematuria; renal compromise	Augmentation cystoplasty; cystectomy with ileal conduit

Table 2. Clinical progression of ketamine-induced cystitis
Adapted from Wu et al. (20) and Zhou et al. (17). LUTS: Lower urinary tract symptoms, NSAIDs: Non-steroidal anti-inflammatory drugs.

Line of therapy	Intervention	Evidence
First-line	Ketamine cessation	Symptoms improvement in ~51% with cessation alone (18)
Oral pharmacotherapy	NSAIDs (ibuprofen 400–600 mg q6–8h; ketorolac 15–30 mg IV)	First-line for reduction of pain and inflammation (17)
	Oxybutynin 5 mg TID	Reduces urgency/frequency (17)
	Prednisone 50 mg daily × 7 days	Reduces acute inflammation (17)
	Pentosan polysulfate 100 mg TID	Only FDA-approved agent for IC; restores GAG layer, protects urothelium (15,17, 20)
Intravesical	Hyaluronic acid; BoNT-A; chondroitin sulfate	For pharmacologic-resistant cases (17)
Surgical	Hydrodistension; augmentation cystoplasty; cystectomy	End-stage disease (15, 17,20)

Table 3. Stepwise management of ketamine-induced cystitis
BoNT-A: Botulinum toxin A, NSAIDs: Non-steroidal anti-inflammatory drugs, q6–8h: every 6 to 8 hours, TID: three times daily.

Pathophysiology

Ketamine and its metabolites—particularly norketamine, generated by hepatic CYP enzymes (CYP2B6, CYP3A4, and CYP2C9)—undergo biliary excretion and concentrate within the biliary tree (2). This concentrated exposure produces direct toxic injury to the biliary epithelium, initiating a cascade of inflammation, periductal fibrosis, and eventual stricture formation (25). Histopathologically, KAC closely mimics primary sclerosing cholangitis (PSC), demonstrating bile duct injury with periductal concentric fibrosis or fibrous duct obliteration (25). Among recreational ketamine users, a serum alkaline phosphatase level of 113 U/L or higher carries a positive predictive value of 85.4% for biliary anomalies, thus serving as a useful screening threshold (26). The diagnostic features of ketamine-associated cholangiopathy are presented in Table 4.

ED Management and Disposition

The single most important therapeutic intervention is immediate and permanent ketamine cessation, as cessation of ketamine has led to regression of cholangiographic abnormalities and normalization of liver function tests (25,26). Conversely, continued ketamine use can progress to bridging fibrosis, decompensated cirrhosis, and death, even in young patients (26).

The pharmacotherapy in the ED is primarily supportive and includes ursodeoxycholic acid for choleresis and hepatoprotection, and cholestyramine for pruritus (2,25). Stable patients (with no evidence of cholangitis and/or biliary obstruction) may be discharged with gastroenterologsits/hepatologist and addiction medicine follow-up. Admission criteria include acute cholangitis, significant biliary obstruction, coagulopathy, or hemodynamic instability (2,25,26). In advanced disease with progressive biliary fibrosis, liver transplant evaluation may be warranted, though this remains rare (26).

Ketamine Use Disorder

Epidemiology

The overall prevalence of illicit ketamine use varies from region to region, with relatively low rates of 1.7% and 0.7% in the United Kingdom and United States, respectively, but with much higher rates in East Asia (27,28). Due to the illicit nature of the drug, the precise numbers of people using ketamine may be higher than reported. The ketamine-induced euphorigenic effects (“K-hole”) include feelings of detachment from one’s physical environment and losing sense of time, space, balance, and verbal skills, creating an “out-of-body experience” (10).

A 2025 survey of 274 individuals with self-identified KUD found that 68.7% were current users, the average age was 28, and 58.8% carried a diagnosed mental health disorder [8]. The primary initial motivations for ketamine use were dissociation (73%), self-medication (53%), and psychedelic effects (56%), with a mean daily consumption of 2.0 g; treatment-seeking users consumed significantly more (mean 2.67 g/day) (8). For most participants (73%), ketamine was their primary drug of use, and the length of problematic use ranged from 2 months to 10 years (8).

Feature	Findings
Symptoms	Cholestatic jaundice; RUQ pain; pruritus; fatigue; dark urine (25,26)
Laboratory pattern	Markedly elevated ALP and GGT; elevated conjugated bilirubin; mildly elevated transaminases (23)
Imaging (MRCP)	Diffuse extrahepatic bile duct dilatation; smooth contour (unlike PSC); fusiform dilatation (26)
Screening	ALP ≥113 U/L: PPV 85.4% for biliary anomalies in sole ketamine users (26)
Associated findings	Concurrent KIC in ~75%; negative autoantibodies; no IBD (25,26)

Table 4. Diagnostic features of ketamine-associated cholangiopathy
ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, IBD: Inflammatory bowel disease, KIC: Ketamine-induced cystitis, MRCP: Magnetic resonance cholangiopancreatography, PPV: Positive predictive value, PSC: Primary sclerosing cholangitis, RUQ: Right upper quadrant, U/L: Units per liter.

Domain	Key findings
Dependence	Craving (71% during abstinence); compulsive use despite harm (8)
Tolerance	Up to 600% dose escalation (10)
Withdrawal	Cravings (71%), low mood (62%), anxiety (59%), irritability (45%), sleep disturbance (36%), fatigue, abdominal pain, sweating, tremors, hallucinations, delusions (8)
Cognitive impairment	Verbal memory, executive function, working memory, spatial memory, attention (10)
Psychiatric comorbidity	Depression (62%), psychosis (31.8% of chronic users), anxiety, suicidality (8,10)
Multi-system toxicity	KIC (~60%); cholangiopathy (~10%); nasal damage (60%); Gastrointestinal symptoms (8,23)

Table 5. Clinical features of ketamine use disorder
KIC:Ketamine-induced cystitis.

Pathophysiology

The neurochemical basis of ketamine's reinforcing effects involves multiple systems. NMDA receptor blockade disinhibits glutamatergic transmission and increases dopamine efflux in the prefrontal cortex (PFC) and mesolimbic pathways (10). Chronic use produces upregulation of D1 receptor availability in the dorsolateral PFC and downregulation of D2 receptors—a pattern shared with other substance use disorders, including cocaine and methamphetamine (10). Key clinical features of KUD include intense psychological dependence with craving reported by 71% of individuals during abstinence; tolerance requiring up to 600% dose escalation; a defined withdrawal syndrome (Table 5); and persistent neurocognitive deficits affecting verbal memory, executive function, and attention (8,10).

ED Management and Disposition

Ketamine withdrawal can produce clinically significant symptoms, including intense cravings, depressed mood, anxiety, irritability, sleep disturbances, fatigue, abdominal pain, autonomic arousal (sweating, tachycardia, palpitations), tremor, and, in severe cases, hallucinations and delusions (8,10). Of note, assessment for co-ingestions is critical given the high prevalence of polysubstance use—over a quarter of participants in the 2025 survey reported using substances other than ketamine as their primary drug (8).

Acute management of ketamine withdrawal is primarily supportive and includes the administration of sedatives and sympatholytics (29). Benzodiazepines (lorazepam 1–2 mg IV or midazolam 2–5 mg IM) are first-line for agitation, neuromuscular hyperactivity, and autonomic instability. Haloperidol (5 mg IM/IV) is indicated for acute psychotic symptoms. Clonidine (0.1–0.2 mg PO/sublingual) or dexmedetomidine (0.2–0.7 mcg/kg/hr IV) may be added for refractory autonomic hyperactivity, including tachycardia, hypertension, and diaphoresis (2,29).

Currently, there is no FDA-approved pharmacotherapy for KUD. Cognitive-behavioral therapy is the foundational behavioral intervention. Emerging pharmacologic options for craving and relapse prevention include naltrexone (50 mg daily), lamotrigine (titrated to 200–300 mg/day), and combination paliperidone palmitate with bupropion, though evidence remains limited to case reports and small series (Table 6) (29,30). Admission is indicated for ED patients with uncontrolled psychosis, severe withdrawal, hemodynamic instability, or suicidal ideation.

The 2025 survey on individuals with self-identified KUD revealed alarming gaps in the KUD treatment landscape: 43% of those who sought treatment found services not tailored to ketamine, 62% perceived providers had little awareness of ketamine-specific issues, and the most commonly cited barrier among non-treatment-seekers was simply a desire to keep using (60%), followed by fear of stigma (42%) (8).

Category	Intervention	Notes
Behavioral	Cognitive behavioral therapy; ketamine-specific support groups	Foundational non-pharmacologic treatment: support groups rated most effective by 22% of users [8]
Acute withdrawal	Lorazepam 1–2 mg IV PRN; haloperidol 5 mg IM/IV; clonidine 0.1–0.2 mg PO BID–TID	Benzodiazepines are first-line treatment for anxiety/autonomic symptoms [29]
Craving/relapse prevention	Naltrexone 50 mg PO daily; lamotrigine (titrate to 200–300 mg/day); paliperidone palmitate + bupropion (150–300 mg/day)	Emerging evidence; no FDA-approved pharmacotherapy [29,30]

Table 6. Pharmacologic and behavioral approaches to KUD management
BID: twice daily, FDA: Food and Drug Administration, IM: intramuscular, IV: intravenous, KUD: Ketamine use disorder, mg: milligram, mg/day: milligrams per day, PO: by mouth, PRN: as needed, TID: three times daily.

Conclusion

Ketamine remains a powerful and versatile therapeutic in emergency medicine, but its adverse-effect profile extends far beyond transient dissociation. Psycho-perceptual effects are nearly universal with rapid intravenous push, yet they are largely preventable through slow infusion and pre-administration coaching. Ketamine-induced cystitis, cholangiopathy, and use disorder represent progressive, multi-organ toxicities that emergency physicians are uniquely positioned to identify—often before any other clinician encounters these patients. Across all chronic syndromes, ketamine cessation is the single most important therapeutic intervention. The current treatment landscape for KUD is limited, with no FDA-approved pharmacotherapy and widespread gaps in provider awareness and service availability. Early recognition of unique adverse effects of ketamine associated with its chronic use and utilization for pain management in the ED, appropriate acute management, and timely referral to addiction medicine, urology, hepatology, and psychiatry can meaningfully alter the trajectory of these conditions and reduce the burden of ketamine-related harm.

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