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REVIEW

Ketamine uropathy: an update on pathophysiology, complications, and treatment options

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Ketamine is a potent anaesthetic drug that has been used for decades. Ketamine abuse is an increasingly common problem, particularly among young people. Over one quarter of ketamine users will have at least one bothersome urological symptom, with heavier and longer use leading to potentially irreversible damage to the lower and upper urinary tract. Hence, this study carried out a narrative review focusing on ketamine-induced uropathy pathophysiology, clinical presentation, and treatment options. It was found that ketamine uropathy is an inflammatory condition affecting predominantly the bladder but also the upper urinary tracts. A hypersensitivity reaction to the drug has been proposed as the potential pathophysiological mechanism that causes inflammatory reaction, muscle hypertrophy, and non-reversible fibrosis in the advanced stages of the disease. Abstinence from ketamine use is the cornerstone of treatment at any stage of the disease, with effective pain management and psychological support being critical to reduce ketamine seeking behaviours. For mildly symptomatic patients, minimally invasive options such as bladder instillations and intravesical Botox injections can provide symptomatic relief. For more severe cases with refractory symptoms and upper urinary tract involvement, reconstructive urological operations might be necessary, including augmentation cystoplasty, cystectomy, or ureteric reconstruction. Ongoing surveillance of the upper tracts is recommended for both groups of patients. Ketamine induced uropathy is an increasingly prevalent condition, and ketamine abuse should always be inquired about in people with unexplained lower urinary tract symptoms. Adequate information of the public regarding ketamine abuse and early consultation with a urologist might prevent irreversible damage.

Key Words: ketamine uropathy, reconstruction, bladder pain, harm reduction, lower urinary tract symptoms (LUTS)

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Introduction

Ketamine uropathy (KU), also known as ketamine cystitis, is a severe and debilitating urological condition caused by chronic recreational use of ketamine. This is an increasingly growing health concern, especially among young adults, as it can lead to profound urinary symptoms and, in difficult situations, irreversible organ damage.[1–3]

First synthesised in 1962, ketamine is a fast-acting dissociative anaesthetic that acts primarily as a non-competitive antagonist to the N-methyl-D-aspartate (NMDA) receptor.[4,5] It is a lipid-soluble molecule with a large volume of distribution, allowing it to cross the blood-brain barrier to produce its central effects. Ketamine undergoes oxidative metabolism in the liver by cytochrome P450 enzymes primarily. Ketamine and its major active metabolite norketamine have a half-life of approximately 2–4 h, and 90% of metabolites are excreted in the urine, and can be detected in urine for up to 14 days after a single dose.[6,7]

Effects vary depending on its dose and can affect learning and memory. It has been demonstrated to play a role in depression by modulating neurotransmitter systems, including opioidergic, monoaminergic, and muscarinic systems, which can potentiate the effects of gamma-aminobutyric acid synaptic inhibition. Low doses are associated with changes to visual, auditory perceptions, whereas high doses can induce the "K-hole" dissociative phenomenon, which is characterised by changes to consciousness and a mind-body dissociation.[8] It has broad clinical uses in anaesthetics, epilepsy, pain management, and recently in depression.[8] Because of the dissociative and analgesic effect, ketamine has a strong and popular appeal as a recreational drug that can be inhaled, smoked, injected, or ingested, and can be referred to by their street names such as 'K', 'Special K', 'Super K', 'Vitamin K', 'Super acid', 'Jet K', 'Kit Kat', 'Purple', 'Special La Coke', 'Cat valium', and 'Cat tranquilizer'.[9]

The objective of this narrative review is to summarise and critically appraise the current evidence on KU, focusing particularly on pathophysiology, clinical presentation, and management. By highlighting current evidence-backed practices and their limitations, this review aims to help provide a practical framework to support the clinical management of KU.

Methods

We conducted a non-exhaustive narrative review of the literature examining the clinical presentation, underlying pathophysiology, and management strategies of KU. A targeted search of electronic databases, including PubMed and MEDLINE (Ovid) was performed. English-language publications between January 2000 and November 2025 were selected based on search terms such as "ketamine", "ketamine abuse", "recreational ketamine", "ketamine cystitis", "ketamine-associated uropathy", combined with "lower urinary tract symptoms", "urothelial dysfunction", "inflammation", "fibrosis", "pathophysiology", and "treatment".

Epidemiology

The prevalence of ketamine use has been increasing in many Western countries. In the UK, the proportion of 16–59-year-olds reporting drug use increased from 0.3% in 2006/2007 to 0.8% in 2023/2024. For young adults aged 16–24 years old, its use has almost trebled in the same period from 0.8% to 2.9% (see Figure 1).[10] This growing trend is reflected in other countries: in the United States, the prevalence of ketamine use has also increased 81.8% between 2015–2019 and 40% between 2021–2022, and in the Netherlands, adult use has doubled from 0.6% to 1.2% between 2018–2023.[11,12] On the contrary, in Hong Kong, ketamine was reported as the second most commonly used recreational drug after heroin by 2010, with over 2000 reported cases in 2014; however, this has dropped to 528 cases since 2014.[3,13]

Epidemiological data on KU have focused primarily on LUTS experienced in ketamine users. In one study of 1285 ketamine users in the UK, who have not sought medical care, 26.6% of the surveyed participants have reported cystitis-like symptoms.[14] This prevalence is similar to another large-scale web-based survey in USA which reports 28% and 30% in people who have tried ketamine before in their life and people who have used ketamine in the past 6 months respectively.[15] Data from Taiwan have shown more than 50% of ketamine users averaging 2 years of use have reported LUTS.[1]

Pathophysiology

The exact mechanism underlying KU is not fully understood, but a number of interconnected pathways have been proposed.

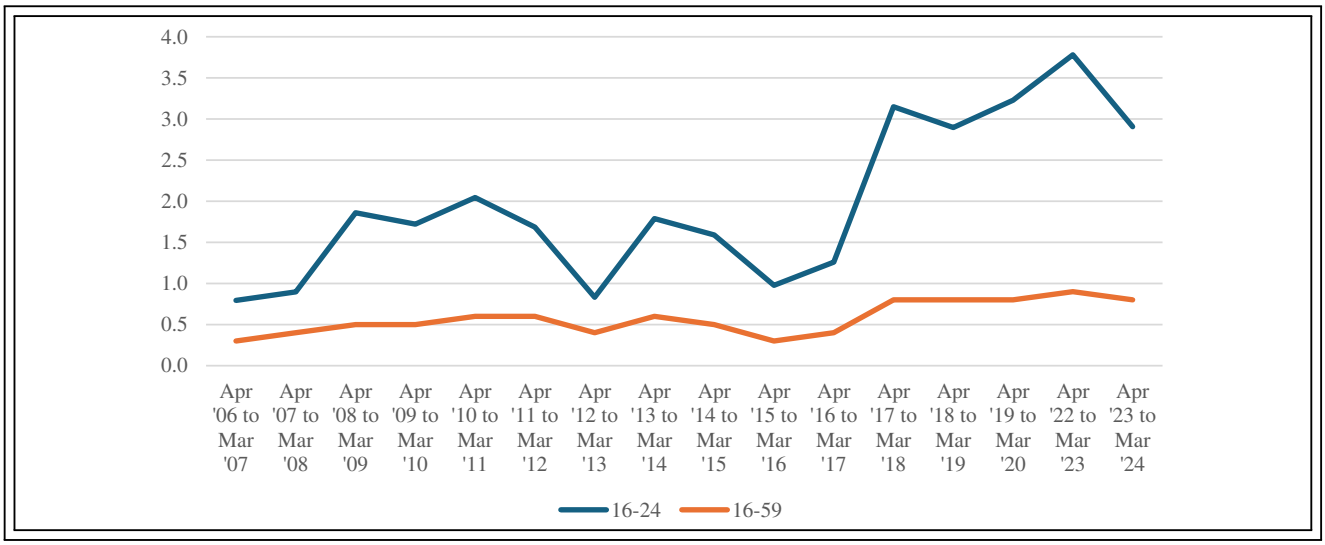

FIGURE 1. Incidence (%) of recreational ketamine use in the United Kingdom from April 2006 to March 2024.[7]

Direct toxicity of ketamine and its metabolites and barrier defects

Ketamine and norketamine exert dose- and exposure-dependent toxicity. Baker et al. demonstrated ketamine-induced apoptosis through mitochondrial and endoplasmic reticulum stress.[16] Concentrations above 1 mmol/L cause a sustained increase in intracellular calcium concentration, activating the intrinsic apoptotic pathway. Ketamine and norketamine can persist in urine for up to 14 days, prolonging drug exposure in the bladder and thereby increasing urothelial toxicity.[1,2,16,17]

Histopathological specimens of the bladder biopsy in KU patients show decreased expression of tight junction and adhesion proteins (zonula occludens-1, E-cadherin, claudin-4, and uroplakins) that are integral for barrier function compared to controls.[1,15] The epithelium becomes permeable, allowing K^+ and ATP to excite the suburothelial afferents and trigger neurogenic inflammation. This results in lowering of depolarisation thresholds, inducing detrusor overactivity. The non-voiding long-term contractions, in addition to TGF-β1-driven fibrosis, progressively reduce bladder compliance.[1]

Hypersensitivity

Transmural inflammation of the bladder involving mast cells and eosinophils predominantly suggests a hypersensitivity mechanism of inflammation.[14,15,17] Patients actively using ketamine show a significantly raised level of IgE, IL-6, and IFN-γ compared to bladder pain syndrome (BPS) or interstitial cystitis (IC), helping to differentiate these two similar conditions. Raised serum IgE levels and eosinophil infiltration of the bladder wall are associated with symptom severity.[18] T-helper cell dysregulation also plays a role, with increased Th2 activity promoting both the production of IgE and T-helper 17 cells that result in further inflammation and collagen deposition.[17]

Microvascular injury

Jhang et al. described microvascular injuries to the bladder. This may be the result of NMDA receptor activation of vascular endothelial cells within the submucosa of the bladder, causing antigen-antibody immune complexes in the arterial walls and subsequent endothelial basement membrane thickening, inflammation, and autoimmune-mediated vascular congestion. This compromises the microcirculation and perfusion to the urothelium, causing ischaemia and pain.[1] Lin et al. demonstrated that the basement membrane is thicker than in healthy controls, suggesting endothelial cell activation and microvascular injury.[19] Histological findings of fibrinoid necrosis within small and medium-sized arterioles of the bladder indicate a possible immune reaction caused by antigen-antibody complex deposition, causing thrombosis, ischaemia, and tissue necrosis and contributing to the severe bladder pain experienced by patients.[20]

Neurogenic inflammation, bladder fibrosis, and upper urinary tract involvement

Nerve hyperplasia is seen in the mucosa, muscle, and subserosa with increased neurotrophin and transforming growth factor-β (TGF-β) signalling.[12,19]

These findings correlate with reduced bladder capacity and pain seen in KU and contribute to the functional changes of hypersensitivity and detrusor overactivity.

Bladder fibrosis is driven by chronic inflammation and collagen deposition. Muscle and subserosal inflammation lead to increased cytokine expression and subsequent collagen deposition in stromal layers, resulting in reduced bladder capacity and fibrosis. In mouse models, fibrosis has been correlated with overexpression of TGF-β1 and fibronectin.[2] Irreversible scarring occurs by cellular transition processes, with TGF-β1 overexpression activating endothelial-to-mesenchymal transition (EMT).[1,2,21,22] Exposed mesenchymal cells due to barrier loss activate fibroblasts via EMT and cause collagen deposition, muscular hypertrophy, and subserosal fibrosis.

In advanced KU, transmural inflammation and fibrosis are not limited to the bladder and can involve the distal ureters, causing ureteric narrowing, oedema, and stricturing with resultant ureteric obstruction.[3] High intra-vesical pressures due to poorly compliant, contracted bladders can overcome the vesicoureteric junction and result in vesicoureteric reflux. The can then result in hydronephrosis and papillary necrosis, and eventual renal failure.[2]

Clinical Presentations

Hallmark symptoms of KU can be any of the following: frequency, urgency, urge urinary incontinence, nocturia, dysuria, suprapubic or loin pain, visible or non-visible haematuria. Urinalysis is usually positive for blood, and urine culture is often negative for bacterial growth. Functional bladder capacity may be reduced. Upper urinary tract involvement, including hydronephrosis and subsequent renal impairment, can occur in advanced disease. Common bile duct dilatation, causing cholangiopathy and liver fibrosis, is also a recognised feature of KU.[2,23] Other clinical findings may also include erectile dysfunction and neurocognitive impairment.[2,24]

The presence of urinary symptoms among ketamine users is dependent on several factors, such as frequency, dose, and duration. Estimates suggest that over one quarter of ketamine users suffer lower urinary tract symptoms (LUTS), and up to 30% will develop some degree of hydronephrosis with prolonged use.[24,25]

A research questionnaire from November 2009 to January 2010 by Winstock et al. described the clinical symptoms of recreational ketamine users to be the following: lower abdominal pain, burning sensation when urinating, increased urinary frequency, urinary incontinence, and haematuria.[26] Symptom severity was associated with increased exposure and dose of ketamine; all patients using more than 5 g/day developed symptoms.[27] Li et al. showed a positive correlation between duration of use and severity of LUTS and bladder pain in a Taiwanese cohort in 2019.[28] Symptoms can appear within one month of use.[23] Mode of administration is also relevant, whereby nasal inhalation is associated with more severe symptoms compared to smoking or oral ingestion.[28] Importantly, reported LUTS severity is not indicative of upper urinary tract involvement or injury.[2]

Many patients do not seek medical attention for KU, with symptoms becoming more apparent after two years of ongoing chronic use.[26,29] Although abstinence is part of the treatment of KU, with 51% of urinary symptoms improving after stopping use, symptoms may still persist for up to 1 year following cessation, with gradual improvement.[2,26]

The advent of ketamine as part of the treatment for treatment resistant depression (TRD) and major depression disorder (MDD) has given rise for the investigation of KU in this patient population. Specifically, esketamine has been approved by the Food and Drug Administration (FDA) for treatment of TRD and MDD and comprises of the isolated S-enantiomer of ketamine compared to racemic ketamine that is used in recreational setting. Esketamine has 3–4 higher affinity for the NMDA receptor and exerts less effect on other pathways that can contribute to KU e.g., opioid, dopaminergic pathways. In the 2025 systematic review of 27 studies of ketamine and esketamine used in psychiatric disorders, Kerr-Gaffney et al. showed that urological symptoms occurred in 0–24.5% of patients and that these symptoms resolved with cessation.[30] These symptoms were mild and rarely required stopping therapy. While chronic recreational use of ketamine is associated with KU, the evidence suggests that therapeutic doses of esketamine is associated with predominantly mild and transient symptoms and has not shown to progress to irreversible uropathy.

The British Association of Urological Surgeons (BAUS) consensus statements on the management of ketamine uropathy in 2024 provide a structured evaluation for a patient suspected of KU.[24] All patients require assessment of urological symptoms, a recreational drug history including ketamine and any other drugs, and the psychosocial impact of symptoms and drug use. The dose, duration, and route of drug use should be noted. An examination of the

abdomen and pelvis should be performed. Investigations also include urinalysis, flow rate, and post-void residual urine volume scan, blood tests for full blood count, renal and liver function, and an ultrasound of the upper urinary tracts. Validated questionnaires such as the pain and urgency/frequency (PUF) questionnaire or the International Consultation on Incontinence Questionnaire ICIQ-LUTS can be used for assessing symptoms of KU.[24,31]

Visible haematuria should be investigated appropriately with cystoscopy with or without a bladder biopsy. Any hydronephroses or suspicion of upper urinary tract involvement would warrant further investigations such as MAG3 renogram, CT urogram, and video urodynamics. Similar diagnostic investigations are proposed by other associations, including the French Association of Urology guidelines for ketamine uropathy.[32]

Without a disclosure of recreational ketamine use history, KU symptoms such as haematuria and severe LUTS can overlap with other conditions, such as UTI and malignancy.[29] Oxley et al. had found histopathological overlap between carcinoma *in situ* (CIS) and KU bladder biopsies. The absence of cytokeratin 20 (CK20) in KU bladder biopsies supports reactive atypia and excludes malignancy.[33]

The BAUS 2024 consensus stratifies KU into 3 stages based on the period and intensity of abuse, renal and liver function derangement, structural or morphological bladder alterations, and upper tract involvement. These stages are adapted from the staging system proposed by Wu et al.[24,34]:

- Stage 1—Predominantly inflammatory changes
- Stage 2—Structural bladder changes (reduced capacity and bladder wall thickening)
- Stage 3—End-stage disease with upper tract involvement

Management of KU

Conservative/bladder-sparing management of KU

Medical management: abstinence, analgesia, and oral pharmacotherapy

Complete ketamine cessation is the first and essential step in conservative care. Ideally, this should be supported by addiction services and combined with symptom control and preservation of bladder capacity and compliance. A large UK study demonstrated that 51% of patients with uropathy symptoms demonstrate improvement after ketamine cessation, as monotherapy.[26] For early stages of the disease, a conservative bundle of urgent ketamine cessation, multimodal analgesia, and oral pharmacotherapy has been suggested.[24,25] For patients using esketamine for TRD or MDD, new onset LUTS should prompt discussion on the risks and benefits of continuing treatment, highlighting the potential long term effects of ketamine on the urinary tract and offer alternative treatment if possible.

Patients with storage symptoms predominant phenotype—as a result of mucosal barrier failure, inflammatory sensitisation of afferent innervation, detrusor overactivity, fibrosis, and subsequent low bladder compliance—could be managed with oral pharmacotherapy using anti-cholinergics and/or without beta-3 agonists.[24,32] Anti-cholinergics lack KU-specific randomised evidence and appear unreliable in established, painful low-compliance bladders, but they are suitable to try in early, less fibrotic KU phenotypes (stage 1–2).[35,36] Non-response should trigger timely escalation to minimally invasive options (intravesical instillations) rather than prolonged dose-cycling.

A hallmark of KU is severe and debilitating bladder pain, and given the proven analgesic benefits of ketamine, a vicious cycle is often created whereby patients continue to use ketamine, or even increase their use to self-medicate for pain control.[29] This sustained ketamine use, therefore, increases the severity of their underlying disease and symptoms. Good pain management is particularly challenging in this cohort, as persistent ketamine misuse has been shown to alter typical pain modulation.[37] There is evidence that tissue from KU bladders demonstrates peripheral nerve fascia hyperplasia and an abundance of neurofilament protein (NFP+) nerve fibres compared to other bladder conditions, a potential mechanism behind the severity of pain experienced by those suffering.[38] Equally, it is well researched that chronic ketamine use increases systemic levels of brain-derived neurotrophic factor (BDNF), an established modulator in both neuropathic pain and inflammatory hypersensitivity. Elevated BDNF levels have therefore been implicated in both chronic pain conditions and a lower pain threshold.[39,40]

Real-world outcomes further attributing to the initial management approach come from Hong Kong's standardised four-tier program.[41] Based on this, first-line oral therapy with anti-inflammatory or anti-cholinergic with or without non-opioid analgesics demonstrated significant improvement in symptoms, with only 19.3% requiring proceeding on second-line treatment (most commonly opioids and pregabalin). Subsequently, 67.7% of the patients requiring the second-line analgesia reported symptomatic

improvement. However, long-term opioid-based regimens remain controversial due to their higher risk of abuse or overdose, especially in this population. For this reason, BAUS suggests a multidisciplinary approach in liaison with the pain team. An analgesic escalation ladder of NSAIDS, COX-2 inhibitors (e.g., etoricoxib), opioid and neuroleptic agents (e.g., amitriptyline, gabapentin, and pregabalin) is recommended.[24]

In the absence of ketamine-specific randomised trials, the American Urological Association (AUA) 2022 guidelines can be adopted in further management of the pain. Amitriptyline, cimetidine, hydroxyzine, and pentosan polysulfate (PPS) are also described as oral options without a specific hierarchy. In a multicentre randomised controlled trial (RCT), amitriptyline plus standardized behavioural therapy did not outperform placebo on an intention-to-treat basis. However, patients titrated to ≥50 mg/day achieved a higher response (66%) than placebo, consistent with the benefit in a subset that tolerates dose escalation.[42] Another RCT demonstrated superiority of amitriptyline over placebo (63% improvement in the treatment group vs. 4% in the placebo one) on lower doses (starting at 25 mg) titrated up to 100 mg daily, if tolerated.[43]

Cimetidine (400 mg twice daily) significantly improved total symptoms, pain, and nocturia vs. placebo in a double-blind RCT.[44] Similarly, two observational series showed 44–57% clinically meaningful improvement at up to 2 years, with minimal adverse events, confirming its applicability in pain management.[45,46] Hydroxyzine has low-quality/heterogeneous evidence (including a pilot trial showing low global response rates when combined with PPS) and demonstrated better efficacy in patients with systemic allergies, likely due to its properties, as a H_1-receptor antagonist, on inhibition of mast cell-mediated response.[47,48]

PPS, an oral glycosaminoglycan (GAG) replacement agent, can also be considered as an adjunct in conservative, bladder-sparing management of early (before fibrosis) KU, with appropriate counselling, follow-up, and alongside abstinence support. In KU, there are no randomised, ketamine specific trials of oral PPS, so its use is justified based on its efficacy on interstitial cystitis/bladder pain syndrome (IC/BPS) and is framed as an individualised, low-certainty option in the current guidelines. This is reported by Shahani et al., where 7 patients had shown improvement following PPS treatment and ketamine cessation.[49] The BAUS 2024 ketamine consensus suggests PPS at the time of cessation in stage 1–2 disease, while French national guidelines (2024) include PPS alongside abstinence, hydrodistention, and onabotulinum toxin A injections before reconstruction as a last resort.[24,32] AUA 2022 guidance recommends PPS as a non-hierarchical option among others, as mentioned above, for the control of IC/BPS, while EAU chronic pelvic pain guidelines, being more conservative, do not preferentially recommend PPS, as they provide stronger direction on intravesical therapy.[50,51] Efficacy-wise, in a multicentre double-blind RCT (n = 368), PPS 100 mg three times daily vs. 100 mg once daily vs. placebo (24 weeks) did not show clear dose-responsive superiority on the primary endpoint, although some secondary or global measures suggested modest benefit—illustrating heterogeneous, small average effects.[52] Safety counselling is deemed essential; pigmentary maculopathy is a dose-dependent risk requiring baseline and periodic retinal exams; bleeding tendency (weak anti-coagulant effect) with alopecia and gastrointestinal disturbances are also described. Overall, these agents are reasonable to trial in Stage 1-2 KU as part of a multimodal, abstinence-anchored plan, with early escalation to intravesical therapies if response is insufficient.

Intravesical therapy: GAG replenishment and analgesic cocktails

In KU, urothelial barrier failure is driven by direct toxicity of ketamine and its metabolites, with loss of apical GAG layers and downregulation and derangement of tight junction and adhesion proteins. Accordingly, GAG replenishment therapy (hyaluronic acid [HA], chondroitin sulfate [CS]) aims to reconstitute the mucosal barrier, inhibit the adherence of immune complexes, and facilitate the healing process. Mechanistic work in a rat KU model shows HA restores tight-junction proteins and attenuates COX-2/TGF-β1-linked inflammation, supporting barrier repair and symptom relief.[53] Intravesical therapy is the principal bladder-sparing escalation for symptomatic stage 1–2 KU, when abstinence and oral measures fail to demonstrate improvement. Meng et al. in a prospective series, using a regimen of 40 mg/50 mL ×6 weekly and then ×3 monthly HA instillations, demonstrated early significant improvement in pain and voiding symptoms with waning effect once dosing dropped to monthly.[54] A Hong Kong prospective series by Yee et al. also reported significant improvement in the functional bladder capacity and pelvic pain, urgency, frequency (PUF) scores, and reduction of the analgesia requirements, specifically in patients with longer abuse time.[55]

Alkalinized-lignocaine-based cocktails (+/−bicarbonate, +/− short-acting steroid, +/− dimethyl sulfoxide-DMSO) are often combined in different regimens, securing rapid analgesia and anti-inflammatory effect. The two standard regimens that the BAUS 2024 ketamine consensus suggests are the Parsons and modified Whitmore's cocktails.[56,57] In practice, instillations are recommended to be delivered only after cessation of ketamine for >1 month, as a weekly induction (4–6 weeks) followed by spaced monthly maintenance if benefit is demonstrable.[24] This guidance is consistent with the French 2024 guidelines that endorse intravesical therapy within a stepped, bladder-sparing pathway.[32] Non-responders after induction should be escalated promptly to intra-detrusor onabotulinumtoxin A injections (± short, low-pressure hydrodistension), rather than cycling ineffective instillations. Patients with advanced-stage fibrotic, fixed, and small-capacity bladders should be referred early for reconstructive assessment.

Hydrodistension: selective use in KU

In KU, cystoscopic hydrodistension can be used for both diagnostic purpose. There is no proven therapeutic benefit in the long term.[32] Most commonly, it is used to assess the bladder capacity, but in selected cases, it can provide short-term analgesic effects and modest capacity increase. When done, it is essential to maintain low pressures and short duration (typical practice: 60–80 cmH_2O for ≤10 min), one or two cycles, to prevent mucosal tears, extravasation, perforation, and a significant flare of bladder symptoms.[50] Active ulceration or infection are relative contraindication. Symptom relief, if achieved, is typically temporary (weeks to a few months) when paired with other measures (e.g., intra-detrusor onabotulinumtoxin A), which is why hydrodistension remains after instillations in the treatment algorithm and is not a stand-alone solution.[51,58]

Onabotulinumtoxin A (BoNT-A) intra-detrusor injections

For abstinent KU patients with refractory urgency or pain after trials of bladder instillation, BoNT-A is the next escalation option. BoNT-A is a potent neurotoxin that inhibits the neurotransmitter release from afferent and efferent nerves and urothelium, leading to peripheral desensitisation and an anti-inflammatory effect. In IC/BPS AUA 2022 and EAU 2024 guidelines recommend it as the last minimally invasive option in cases of instillation failures.[50,59] This intervention is extended to KU since both IC/BPS and KU share common inflammatory and neurogenic mechanisms. BAUS 2024 and the French Association of Urology 2024 guidelines have also included it in their KU management pathways.[24,32] Zeng et al. reported that 200 U BoNT-A combined with low-pressure hydrodistension produced marked symptom relief at 1 month with significant improvements in interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI), voiding interval, voided volume, Q_{max}, and bladder capacity.[60] One RCT demonstrated that BoNT-A (200 U) with HA is superior to hydrodistension and HA at 12 months for daytime frequency, ICSI, and maximal cystometric capacity, supporting both efficacy and durability.[58] Noteworthy, patients should be counselled about transient urinary retention (requires in advance teaching of intermittent self-catheterisation), UTI risk, and the need for repeat cycles (benefit commonly 3–6, sometimes up to 9 months). Very low-capacity, fibrotic bladders (stage 3) respond poorly and should be considered early for reconstructive pathways rather than repeated injections.

Urinary tract reconstruction in KU

Major reconstructive surgical options are usually reserved for a selected group of patients with KU. These typically include motivated patients who have been abstinent for at least 6 months and have failed pharmacotherapy and minimally invasive treatments or present with end-stage bladder dysfunction and upper tract compromise.[2] There are no strict criteria to determine the optimal timing of urological reconstruction, or the exact type of reconstructive surgery, and the available evidence is currently limited to small retrospective series. Therefore, the operation of choice should be decided on an individualised basis and be validated by a multi-disciplinary team of experts, including surgeons, pain specialists, and psychologists.[24] Most series reporting cases treated with reconstructive surgery include patients with severely contracted bladders (capacity <100 mL), hydronephrosis, vesicoureteric reflux (VUR), or renal impairment.[61,62] In such cases, reconstructive surgery seems to be the only safe option, preferred to bladder sparing treatments, which have usually been tried and failed. The ultimate aim of reconstructive surgery in this patient group is to create a low-pressure, compliant reservoir in order to minimise the risk of renal impairment and diminish the abnormal, painful bladder sensation and urgency symptoms.[63]

Patients considered for major reconstructive surgery should undergo a detailed pre-operative assessment as detailed in previous sections. Cystoscopic assessment of the bladder with or without biopsy is useful to exclude concurrent

abnormalities and measure anatomical bladder capacity. Video urodynamics is essential for the assessment of bladder compliance and the presence of VUR.[25] A critical factor that affects the surgical plan is the possibility of ureteric stricture. Therefore, investigations to assess the upper tracts, including renal ultrasonography, CT IVU, or retrograde ureteropyelogram at the time of cystoscopic assessment, are necessary before proceeding to major surgery.[32]

A variety of surgical operations have been reported in the literature, including augmentation enterocystoplasty (with or without supratrigonal cystectomy) with preservation of the trigone and bladder neck, total cystectomy with orthotopic or heterotopic neobladder formation, and urinary diversion with ileal conduit formation. If there is evidence of ureteric involvement, then excision of the diseased ureteric segment and ureteric reimplantation or reconstruction may be necessary.[64] These operations have most commonly been performed through an open approach; however, there are increasing reports of a minimally invasive approach (i.e., robot-assisted) in this patient population.[65]

Lee et al. reported a retrospective series of 26 patients with advanced KU presenting with significantly contracted bladders (bladder capacity <100 mL), hydronephrosis, or VUR, who were treated with augmentation enterocystoplasty with or without ureteric reimplantation. Overall, there was significant improvement in urodynamic parameters (bladder capacity, compliance, voided volumes), self-reported symptoms, and resolution or improvement of hydronephrosis and VUR. However, 10 patients who resumed ketamine abuse after surgery presented with symptom recurrence.[62] Similar good outcomes were reported by Chung et al., who reported 14 cases of end-stage KU in Taiwan, treated with augmentation enterocystoplasty. All patients had significant subjective and objective improvement in symptoms and urodynamic parameters, respectively, but symptom recurrence was associated with ketamine use post-operation in 4 patients.[61] As expected, in patients having cystoplasty surgery, increased post-void residual and the need to perform self-catheterisation were reported in these series, although all patients were able to void spontaneously after surgery.[61,62]

It must be noted that case series demonstrated a high complication rate in this cohort of patients when compared to patients having similar operations for other benign conditions, such as neurogenic lower urinary tract dysfunction, intractable incontinence, or IC/BPS. Sihra et al. reported a cohort of 44 patients, of which 14 underwent major reconstructive surgery, including augmentation cystoplasty, cystectomy, and neobladder (with or without Mitrofanoff channel formation), and ileal conduit urinary diversion. Eight of the 14 patients had good long-term outcomes with resolution of pain and hydronephrosis, and stable renal function; however, 10 patients had post-operative complications requiring surgical intervention, including urine and bowel leaks, new ureteric strictures, and renal impairment.[66] Similarly, Ng et al. reported worsening renal function in 3 out of 4 patients treated with augmentation cystoplasty despite the initial improvement in symptoms and bladder capacity. This deterioration was associated with new-onset ureteric strictures post-surgery in 2 patients.[67]

In conclusion, major reconstructive surgery is likely the only option in end-stage ketamine uropathy. However, it is associated with high morbidity and should be reserved only for selected patients who have demonstrated abstinence and are committed, as recurrence of symptoms has been consistently reported with ketamine relapse.

Psychological support for ketamine cessation

As mentioned already, the cornerstone of effective ketamine uropathy treatment is ketamine cessation. Alongside conservative or operative management, effective addiction and substance misuse treatment is essential, as ketamine relapse is associated with symptom deterioration even after major reconstructive surgery.[61,62] There is a paucity of research on ketamine withdrawal symptoms and specific addiction treatments. There is also a lack of services available to patients looking for support in ketamine endemic areas globally. Harding et al. in 2025, from surveying ketamine users from the UK, USA, Canada, and Europe, reported that treatment-seeking patients found that services generally had a poor understanding of ketamine use, were not tailored to ketamine use, or were largely ineffective.[68]

Various pharmacological and neurological therapies have been implicated in aiding ketamine use disorder treatment, including naltrexone, NMDA receptor modulators, and transcranial magnetic stimulation therapy, but all studies thus far have been small or case study cohorts with descriptive outcomes and with no large-scale trials to date.[69–71]

More psychological treatment options are better established for substance addiction management; however, there is minimal data on ketamine specific treatments. Interventions, including brief interventions, motivational interviewing, and cognitive behavioural therapy programmes, have

all been shown to be cost-effective options to treat substance misuse disorders compared to inactive control groups.[72] However, few studies and trials have significant follow-up periods, so little is known if benefits are long-lasting.[73]

Many substance misuse programmes now focus on a combination of pharmacological and psychological therapies. Benzodiazepines have been implicated in the treatment of ketamine abuse when combined with talking therapies, which have shown periods of sustained abstinence and reduced ketamine intake during periods of relapse, but again, all current research remains at a case study level.[74] The use of ketamine is increasing as the addiction research community and mental health professionals have become more interested in ketamine as a treatment option for other substance disorders or depression.[75] Although the side effects of the use of ketamine for those indications have not been followed up in the long term, it is evidently clear that there is a further need to develop ketamine specific treatment programmes for existing KU patients in order to reduce and prevent progression of the disease.

Limitations

This review is narrative in nature and follow the conclusions of selected literature available on KU, some of which include small case series, single-centre cohorts, or retrospective studies. Randomised controlled trials are lacking and long term follow up data on patients evaluating disease progression, treatment response, and renal outcomes are limited. Many of the published evidence arise from East Asia, where it has been historically prevalent. Differences in patient demographics, ketamine use and behaviour, access to healthcare, and referral pathways are not similar and may not be generalizable in other countries. There is also no universally accepted diagnostic criteria or staging system for KU, when there is a spectrum of disease presentation in KU; comparison between different cohorts and outcomes challenging to compare.

Conclusions

KU is a progressive and painful condition that results from chronic ketamine misuse. The pathophysiology involves direct urothelial injury, hypersensitivity-driven inflammation, neurogenic remodelling and microvascular injury, which culminates in bladder fibrosis, reduced bladder capacity and compliance, and in severe cases, renal failure. The reversibility of symptoms is dependent on early recognition and cessation, and those with advanced disease will often require major reconstructive surgery.

A multidisciplinary team approach alongside shared decision-making and tailored psychosocial support is crucial in the effective management of KU. Early diagnosis, counselling, and referral to abstinence services and support groups can limit the progression of the disease, while bladder-sparing and symptomatic therapies help minimize the symptom severity and reduce the risk of drug relapse. Regular follow-up and monitoring of renal function are pragmatically offered, with prompt and timely referral for reconstructive assessment when symptom relief is not achieved or when there is upper urinary tract involvement, provided drug abstinence has been achieved.

The challenges of effective KU management are multifaceted and well-documented. The scarcity of robust trials comparing pharmacological and reconstructive interventions highlights the need for further research. Future studies should focus on further understanding the pathogenesis of KU, targeted therapies, and the design of effective addiction treatment programmes.

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Availability of Data and Materials

Not applicable.

Ethics Approval

This study used only published data and did not involve human or animal subjects; therefore, ethical approval was not required.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Jhang JF, Birder LA, Kuo HC. Pathophysiology, clinical presentation, and management of ketamine-induced cystitis. *Tzu Chi Med J* 2023;35(3):205–212.
2. Castellani D, Pirola GM, Gubbiotti M et al. What urologists need to know about ketamine-induced uropathy: a systematic review. *Neurourol Urodyn* 2020;39(4):1049–1062.
3. Chu PS, Ma W, Wong SC et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008;102(11):1616–1622.
4. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet* 2016;55(9):1059–1077.
5. Yavi M, Lee H, Henter ID, Park LT, Zarate CA Jr. Ketamine treatment for depression: a review. *Discov Ment Heal* 2022;2(1):9.
6. Zanos P, Moaddel R, Morris PJ et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev* 2018;70(3):621–660.
7. Parkin MC, Turfus SC, Smith NW et al. Detection of ketamine and its metabolites in urine by ultra high pressure liquid chromatography-tandem mass spectrometry. *J Chromatogr B* 2008;876(1):137–142.
8. Morgan CJ, Curran HV. Ketamine use: a review. *Addiction* 2012;107(1):27–38. doi:10.1111/j.1360-0443.2011.03576.x.
9. DEA. Ketamine [Internet]. Arlington, VA, USA: United States Drug Enforcement Administration; 2019 [cited 2026 Feb 11]. Available from: https://www.dea.gov/factsheets/ketamine.
10. Office for National Statistics. Drug misuse in England and Wales: year ending March 2020 [cited 2026 Feb 11]. Available from: https://www.ons.gov.uk/releases/drugmisuseinenglandandwalesyearendingmarch2020.
11. Marongiu S, van Eijk M, Gresnigt FMJ, Croes EA, Franssen EJF. Rising incidence of recreational ketamine use: clinical cases and management in emergency settings. *Toxicol Rep* 2025;14(1):101940.
12. Yang KH, Kepner W, Cleland CM, Palamar JJ. Trends and characteristics in ketamine use among US adults with and without depression, 2015–2022. *J Affect Disord* 2025;373(6):345–352.
13. Narcotics Division, Security Bureau. Main charts/tables [Internet]. [cited 2026 Feb 11]. Available from: https://www.nd.gov.hk/en/crda_main_charts_and_tables.html.
14. Jhang J, Hsu Y, Jiang Y, Lee C, Kuo H. Histopathological characteristics of ketamine-associated uropathy and their clinical association. *Neurourol Urodyn* 2018;37(5):1764–1772.
15. Lee C, Jiang Y, Kuo H. Increased apoptosis and suburothelial inflammation in patients with ketamine-related cystitis: a comparison with non-ulcerative interstitial cystitis and controls. *BJU Int* 2013;112(8):1156–1162.
16. Baker SC, Shabir S, Georgopoulos NT, Southgate J. Ketamine-induced apoptosis in normal human urothelial cells: a direct, N-methyl-d-aspartate receptor-independent pathway characterized by mitochondrial stress. *Am J Pathol* 2016;186(5):1267–1277.
17. Fan GY, Cherng JH, Chang SJ et al. The immunomodulatory imbalance in patients with ketamine cystitis. *Biomed Res Int* 2017;2017(1):2329868.
18. Jhang JF, Hsu YH, Jiang YH, Kuo HC. Elevated serum IgE may be associated with development of ketamine cystitis. *J Urol* 2014;192(4):1249–1256.
19. Lin CC, Lin ATL, Yang AH, Chen KK. Microvascular injury in ketamine-induced bladder dysfunction. *PLoS One* 2016;11(8):e0160578.
20. Chen Y, Jhang J, Hsu Y, Kuo H. Vascular fibrinoid necrosis in the urinary bladder of ketamine abusers: a new finding that may provide a clue to the pathogenesis of ketamine-induced vesicopathy. *LUTS Low Urin Tract Symptoms* 2019;11(2):O221–O223.
21. Jhang J, Wang H, Hsu Y, Birder LA, Kuo H. Upregulation of neurotrophins and transforming growth factor-β expression in the bladder may lead to nerve hyperplasia and fibrosis in patients with severe ketamine-associated cystitis. *Neurourol Urodyn* 2019;38(8):2303–2310.
22. Wang J, Chen Y, Gu D et al. Ketamine-induced bladder fibrosis involves epithelial-to-mesenchymal transition mediated by transforming growth factor-β1. *Am J Physiol Physiol* 2017;313(4):F961–F972.
23. Tsai YC, Kuo HC. Ketamine cystitis: its urological impact and management. *Urol Sci* 2015;26(3):153–157.
24. Belal M, Downey A, Doherty R et al. British association of urological surgeons consensus statements on the management of ketamine uropathy. *BJU Int* 2024;134(2):148–154.
25. Hervé F, Aronsson P, Ochoa DC et al. Can we better understand, diagnose, and treat ketamine-induced uropathy, and can it be reversed? ICI-RS 2024. *Neurourol Urodyn* 2025;44(3):548–557.
26. Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. *BJU Int* 2012;110(11):1762–1766.
27. Cottrell A, Warren K, Ayres R, Weinstock P, Gillatt DA. The relationship of chronic recreational ketamine use and severe

bladder pathology: presentation, management of symptoms and public health concerns. *Eur Urol Suppl* 2009;8(4):170.
28. Li CC, Wu ST, Cha TL, Sun GH, Yu DS, Meng E. A survey for ketamine abuse and its relation to the lower urinary tract symptoms in Taiwan. *Sci Rep* 2019;9(1):7240.
29. Wood D, Cottrell A, Baker SC et al. Recreational ketamine: from pleasure to pain. *BJU Int* 2011;107(12):1881–1884.
30. Kerr-Gaffney J, Tröger A, Caulfield A et al. Urological symptoms following ketamine treatment for psychiatric disorders: a systematic review. *J Psychopharmacol* 2025;39(10):1103–1113.
31. Ng CM, Ma WK, To KC, Yiu MK. The Chinese version of the pelvic pain and urgency/frequency symptom scale: a useful assessment tool for street-ketamine abusers with lower urinary tract symptoms. *Hong Kong Med J* 2012;18(2):123–130.
32. Bourillon A, Cornu JN, Herve F et al. Management of ketamine cystitis: national guidelines from the French Association of Urology (CUROPF/CTMH). *French J Urol* 2024;34(14):102754.
33. Oxley JD, Cottrell AM, Adams S, Gillatt D. Ketamine cystitis as a mimic of carcinoma *in situ*. *Histopathology* 2009;55(6):705–708.
34. Wu P, Wang Q, Huang Z, Wang J, Wu Q, Lin T. Clinical staging of ketamine-associated urinary dysfunction: a strategy for assessment and treatment. *World J Urol* 2016;34(9):1329–1336.
35. Jhang J, Hsu Y, Kuo H. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. *Int J Urol* 2015;22(9):816–825.
36. Tsai T, Cha T, Lin C et al. Ketamine-associated bladder dysfunction. *Int J Urol* 2009;16(10):826–829.
37. Anderson DJ, Zhou J, Cao D et al. Ketamine-induced cystitis: a comprehensive review of the urologic effects of this psychoactive drug. *Heal Psychol Res* 2022;10(3):38247.
38. Baker SC, Stahlschmidt J, Oxley J et al. Nerve hyperplasia: a unique feature of ketamine cystitis. *Acta Neuropathol Commun* 2013;1(1):64.
39. Ricci V, Martinotti G, Gelfo F et al. Chronic ketamine use increases serum levels of brain-derived neurotrophic factor. *Psychopharmacology* 2011;215(1):143–148.
40. Xiong HY, Hendrix J, Schabrun S et al. The role of the brain-derived neurotrophic factor in chronic pain: links to central sensitization and neuroinflammation. *Biomolecules* 2024;14(1):71.
41. Yee C-H, Lai P-T, Lee W-M, Tam Y-H, Ng C-F. Clinical outcome of a prospective case series of patients with ketamine cystitis who underwent standardized treatment protocol. *Urology* 2015;86(2):236–243.
42. Foster HE, Hanno PM, Nickel JC et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. *J Urol* 2010;183(5):1853–1858.
43. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol* 2004;172(2):533–536.
44. Thilagarajah R, Witherow RO, Walker MM. Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001;87(3):207–212.
45. Dasgupta P, Sharma SD, Womack C, Blackford HN, Dennis P. Cimetidine in painful bladder syndrome: a histopathological study. *BJU Int* 2001;88(3):183–186.
46. Seshadri P, Emerson L, Morales A. Cimetidine in the treatment of interstitial cystitis. *Urology* 1994;44(4):614–616.
47. Sant GR, Propert KJ, Hanno PM et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol* 2003;170(3):810–815.
48. Theoharides TC. Hydroxyzine in the treatment of interstitial cystitis. *Urol Clin North Am* 1994;21(1):113–119.
49. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007;69(5):810–812.
50. Clemens JQ, Erickson DR, Varela NP, Lai HH. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2022;208(1):34–42.
51. EAU Guidelines. Edn. presented at the EAU Annual Congress, Madrid 2025.
52. Nickel JC, Herschorn S, Whitmore KE et al. Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. *J Urol* 2015;193(3):857–862.
53. Lee YL, Lin KL, Chuang SM et al. Elucidating mechanisms of bladder repair after hyaluronan instillation in ketamine-induced ulcerative cystitis in animal model. *Am J Pathol* 2017;187(9):1945–1959.
54. Meng E, Tsao CW, Tang SH et al. Intravesical hyaluronic acid treatment for ketamine-associated cystitis: preliminary results. *Urol Sci* 2015;26(3):176–179.
55. Yee CH, Hong CYL, Lai FPT, Tam YH, Ng CF. Effect of intravesical hyaluronic acid instillation on ketamine-induced cystitis: MP39-09. *J Urol* 2018;199(4):e513.
56. Parsons CL, Zupkas P, Proctor J et al. Alkalinized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. *J Sex Med* 2012;9(1):207–212.
57. Colemeadow J, Sahai A, Malde S. Clinical management of bladder pain syndrome/interstitial cystitis: a review on current recommendations and emerging treatment options. *Res Rep Urol* 2020;18(12):331–343.
58. Li B, Leng Q, Li C, Tan X, Su W, Li C. Comparison of intravesical instillation of hyaluronic acid with intradetrusor botulinum toxin A injection or cystoscopic hydrodistention for ketamine-associated cystitis. *J Int Med Res* 2020;48(11):0300060520973100.
59. Engeler D, Baranowski AP, Borovicka J et al. EAU guidelines on chronic pelvic pain. Arnhem, The Netherlands: European Association of Urology; 2025 [cited 2026 Feb 11]. Available from: https://uroweb.org/guidelines/chronic-pelvic-pain.
60. Zeng J, Lai H, Zheng D et al. Effective treatment of ketamine-associated cystitis with botulinum toxin type a injection combined with bladder hydrodistention. *J Int Med Res* 2017;45(2):792–797.
61. Chung S, Wang C, Kuo H. Augmentation enterocystoplasty is effective in relieving refractory ketamine-related bladder pain. *Neurourol Urodyn* 2014;33(8):1207–1211.
62. Lee YK, Jhang JF, Kuo HC. Clinical outcome of augmentation enterocystoplasty for patients with ketamine-induced cystitis. *Pain Phys* 2017;20(3):E431–E436.
63. Jhang J, Birder LA, Chancellor MB, Kuo H. Patient characteristics for different therapeutic strategies in the management ketamine cystitis. *Neurourol Urodyn* 2017;36(3):687–691.
64. Vizgan G, Huamán M, Rychik K, Edeson M, Blaivas JG. Ketamine-induced uropathy: a narrative systemic review of surgical outcomes of reconstructive surgery. *BJUI Compass* 2023;4(4):377–384.

65. Yee CH, Ko ICH, Tam HM, Wong HF, Lo KL, Hoi-Chak W. Robotic bilateral ileal interposition: the total intracorporeal approach. *Int Braz J Urol off J Brazilian Soc Urol* 2025;51(6):e20250359. doi:10.1590/s1677-5538.ibju.2025.0359.
66. Sihra N, Ockrim J, Wood D. The effects of recreational ketamine cystitis on urinary tract reconstruction-a surgical challenge. *BJU Int* 2018;121(3):458–465.
67. Ng CF, Chiu PKF, Li ML et al. Clinical outcomes of augmentation cystoplasty in patients suffering from ketamine-related bladder contractures. *Int Urol Nephrol* 2013;45(5):1245–1251.
68. Harding RE, Barton T, Niepceron M et al. The landscape of ketamine use disorder: patient experiences and perspectives on current treatment options. *Addiction* 2025;120(10): 1970–1979.
69. Garg A, Sinha P, Kumar P, Prakash O. Use of naltrexone in ketamine dependence. *Addict Behav* 2014;39(8):1215–1216.
70. Hsiao YC, Lee MY, Chan MH, Chen HH. NMDA receptor glycine binding site modulators for prevention and treatment of ketamine use disorder. *Pharmaceuticals* 2023; 16(6):812.
71. Yao CY, Wang YH, Cheng S, Huang SY. Repetitive transcranial magnetic stimulation (rTMS) treatment in ketamine use disorder: a case report. *Asian J Psychiatr* 2022;67: 102912.
72. Jhanjee S. Evidence based psychosocial interventions in substance use. *Indian J Psychol Med* 2014;36(2):112–118.
73. Dellazizzo L, Potvin S, Giguère S, Landry C, Léveillé N, Dumais A. Meta-review on the efficacy of psychological therapies for the treatment of substance use disorders. *Psychiatry Res* 2023;326(6):115318.
74. Critchlow DG. A case of ketamine dependence with discontinuation symptoms. *Addiction* 2006;101(8):1212–1213.
75. Ivan Ezquerra-Romano II, Lawn W, Krupitsky E, Morgan CJA. Ketamine for the treatment of addiction: evidence and potential mechanisms. *Neuropharmacology* 2018;142(20): 72–82.