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Treatment and management approaches for ketamine misuse: A systematic review of medical interventions

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ABSTRACT

Introduction: Ketamine, initially developed as an anesthetic and now increasingly prescribed for treatment-resistant depression, is also widely misused in recreational contexts. Chronic ketamine use, often leading to dependence, has been associated with severe physical complications, including ulcerative cystitis and gastrointestinal dysfunction, as well as cognitive, affective, and psychotic disturbances. Despite the growing clinical and public health relevance of ketamine misuse, the evidence on effective treatment approaches remains fragmented.

Methods: A systematic review was conducted in accordance with PRISMA guidelines. We searched three literature databases (PubMed, Scopus, and Web of Science) from inception to April 2025. Original studies in English reporting clinical interventions for ketamine misuse were included. Data were extracted on sociodemographic and clinical characteristics, patterns of use, comorbidities, management strategies, and outcomes.

Results: From 3183 records screened, 73 studies met the inclusion criteria, including 5 controlled clinical studies, 15 observational studies, 15 case series, and 38 case reports. Findings highlighted that management of ketamine misuse is heterogeneous and often based on evidence taken from either case reports or small series. Approaches included symptomatic medical care, psychotherapeutic interventions (e.g., motivational interviewing, cognitive-behavioral therapy, occupational therapy), and pharmacological treatments such as benzodiazepines, SSRIs, naltrexone, lamotrigine, and gabapentinoids, with varying degrees of effectiveness. Multidisciplinary strategies addressing both psychiatric and somatic complications, including "K-bladder" and "K-cramps", emerged as an essential component of the treatment/management package. Overall, the high rates of relapse into ketamine misuse and the limited length of follow-up may have reduced the strength of available evidence.

Conclusions: Current management of ketamine misuse relies mainly on supportive care, psychotherapy, and off-label pharmacological options, but robust evidence on efficacy is lacking. There is an urgent need for controlled studies and standardized treatment protocols. Integrated, multidisciplinary, models appear most promising in addressing the complex medical and psychiatric consequences of ketamine misuse.

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1. Introduction

The increasing misuse of ketamine (European Union Drugs Agency, 2024; Guerrini et al., 2025) is being observed in a range of recreational contexts, where it is commonly referred to by the street names "K", "Special K", "Vitamin K", and "Super K" (Schifano et al., 2025). These different patterns and severity of ketamine use have been linked to a spectrum of adverse outcomes, including acute intoxication, being frequently characterized by agitation, hallucinations, nausea, tachycardia, and hypertension (Marongiu et al., 2025). With repeated use, ketamine is associated with serious medical complications, most notably ketamine-induced ulcerative cystitis and uropathy (Chiappini et al., 2025; Schifano et al., 2021), alongside cognitive deficits and gastrointestinal disturbances. Although ketamine use disorder (KUD) is increasingly recognized in clinical settings, it is important to note that there are currently no formal, universally accepted diagnostic criteria specifically for KUD, and its identification is generally based on broader substance use disorder frameworks (Chiappini et al., 2025; Marongiu et al., 2025). Ketamine is often misused for its desirable subjective effects, including dissociation, euphoria, perceptual distortions, and emotional detachment. Common motivations for use include recreational purposes (e.g., club settings), self-medication for mood symptoms, and curiosity-driven experimentation (Chiappini et al., 2025; Marongiu et al., 2025; Schifano et al., 2021). From the psychopathological perspective, ketamine misuse has been linked to the onset or exacerbation of mood disorders, psychosis, dissociation, and dependence syndromes (Schifano et al., 2021). These consequences present complex challenges in both acute and long-term care settings (Marongiu et al., 2025). The growing misuse of ketamine coincides with its increasing adoption in clinical practice, particularly for its antidepressant and antisuicidal effects when administered under medical supervision and in association with psychotherapeutic interventions (Chiappini et al., 2025; Fornaro et al., 2021; Kim et al., 2024; Martinotti et al., 2021). Beyond its rapid onset of action, ketamine offers therapeutic benefits for patients with treatment-resistant depression, providing a novel mechanism which may be distinct from conventional antidepressants and thereby expanding the range of available treatment options (Martinotti et al., 2021). However, this expanding clinical use also raises concerns regarding diversion, non-medical use, and misuse risk, particularly outside controlled medical settings and among vulnerable populations (Ingrosso et al., 2025). In addition, some user perspectives suggest that the increasing availability of ketamine in psychiatric settings may contribute to wider non-medical use, although evidence in this area remains limited (Harding et al., 2025). Despite its promise, the wider therapeutic implementation of ketamine remains restricted by several inherent limitations, such as the need of a controlled medical setting, although with this approach the risk of diversion or misuse is minimized as much as possible (Chiappini et al., 2023; Short et al., 2018). Despite the increasing clinical and public health relevance of ketamine misuse and the growing recognition of its psychiatric and somatic complications, evidence on effective treatment and management strategies remains limited and fragmented. Available reports are frequently based on case reports or small series, with heterogeneous interventions and short follow-up, which precludes the development of standardized, evidence-based clinical protocols. A comprehensive synthesis focusing specifically on management approaches and outcomes is therefore needed to inform multidisciplinary care models and identify research priorities.

1.1. Aim of the study

This systematic review aimed at synthesizing current evidence on treatment and management approaches for ketamine misuse, with a specific focus on addressing its physical and psychological consequences.

More specifically, the review aimed at:

1. Identifying and evaluating current treatment strategies for managing ketamine misuse, including both pharmacological and psychotherapeutic interventions.
2. Examining medical consequences associated with chronic ketamine misuse, such as urological, neurological, and cognitive impairments, and assessing how these are managed from the clinical point of view.
3. Exploring psychopathological outcomes, including ketamine-induced mood disorders, psychosis, dependence, and reviewing interventions targeting these conditions.
4. Assessing the effectiveness and limitations of existing management approaches, with the goal of informing evidence-based, multidisciplinary care models.
5. Highlighting research gaps and providing recommendations for future clinical and research directions in the treatment of ketamine misuse.

2. Materials and methods

2.1. Systematic review procedures

On 29 April 2025, the authors systematically searched the PubMed, Scopus, and Web of Science (WoS) literature databases and identified additional relevant papers from the reference lists of the included articles that the database search did not retrieve.

2.2. Search strategy

For PubMed and WoS, the following search string was used: [ketamine AND (abuse OR misuse OR addiction OR abstinence OR withdrawal) AND (treatment OR therapy OR management) NOT (review OR animal)]. A slightly different search strategy was used for Scopus: [TITLE-ABS-KEY(ketamine AND (abuse OR misuse OR addiction OR abstinence OR withdrawal) AND (treatment OR therapy OR management) AND NOT (review OR animal)].

The authors structured the systematic review in accordance with the PRISMA guidelines (Page et al., 2021). The reviewers assessed the identified studies by examining the titles and abstracts (where available) and conducting a full-text screening against the eligibility criteria.

2.3. Eligibility criteria

Studies were considered eligible for inclusion if they met the following criteria:

2.3.1. Inclusion criteria

1) Original research articles of any design providing extractable clinical data on ketamine misuse, ketamine dependence, or ketamine use disorder (KUD) in human subjects.
2) Published in the English language.
3) Reporting at least one clinical intervention or management approach, including: Pharmacological treatments (e.g., craving reduction, withdrawal management, psychiatric symptom control); Psychotherapeutic or behavioral interventions (e.g., motivational interviewing, CBT, family-based therapy); Medical or surgical management of ketamine-related complications (e.g., ketamine-induced bladder dysfunction, hepatobiliary or gastrointestinal complications); Multidisciplinary or rehabilitation programmes.

No restriction was applied regarding patient age, sex, duration of ketamine misuse, or clinical setting.

2.3.2. Exclusion criteria

The reviewers assessed the identified studies by examining the titles and abstracts and conducting a full-text screening against the eligibility criteria:

1) Non-original research (e.g., review, meta-analysis, commentary, editorial, letter to the editor without data available, and book chapter);
2) Non-full-text articles (e.g., meeting abstract);
3) Language other than English;
4) Animal/in vitro studies;
5) Articles not dealing with the misuse of ketamine,
6) Articles without any report on treatment.

2.4. Protocol and registration

Current research methods were approved by PROSPERO (identification code CRD420251043897).

2.5. Data synthesis strategy

The selection and eligibility phases of the articles were carried out independently by R.A., N.C., C.M., and T.P., after having been subjected to a final cross-check by A.M. and A.Mi. All discordant cases were evaluated by S.C. and M.P. Any unsolved doubts by the team on any of the topics covered in the articles were clarified directly from the author, if contactable. Data extraction was performed independently by R.A., N. C., C.M., and T.P. All extracted data were cross-checked by A.M. and A. Mi. Any discrepancies were discussed and resolved with the involvement of S.C. and M.P. The data were collated in a Word table containing the first author's name and year of publication of the study, study design, details on the administration (e.g., dosage and route of administration), demographic variables (e.g., gender, age, psychiatric comorbidity), details on poly-abuse (e.g., substances involved), duration of abuse/dependence, abuse/dependence treatment, symptomatology (e.g., psychiatric symptoms; psychiatric symptoms' treatment; other symptoms), ketamine bladder symptomatology and treatment, k-cramp-related symptomatology (e.g., recurrent abdominal and pelvic pain) and treatment. The recommendations presented in Table 4 and the proposed treatment algorithm (Fig. 2) were derived from a narrative synthesis of the extracted data, integrating evidence on treatment approaches, reported outcomes, and consistency of findings across the included studies. No formal grading of evidence or strength of recommendations was applied, given the predominantly descriptive nature and heterogeneity of the included studies. Therefore, this framework does not represent a formal evidence-based or consensus-driven guideline, but should be interpreted as a pragmatic clinical approach based on the

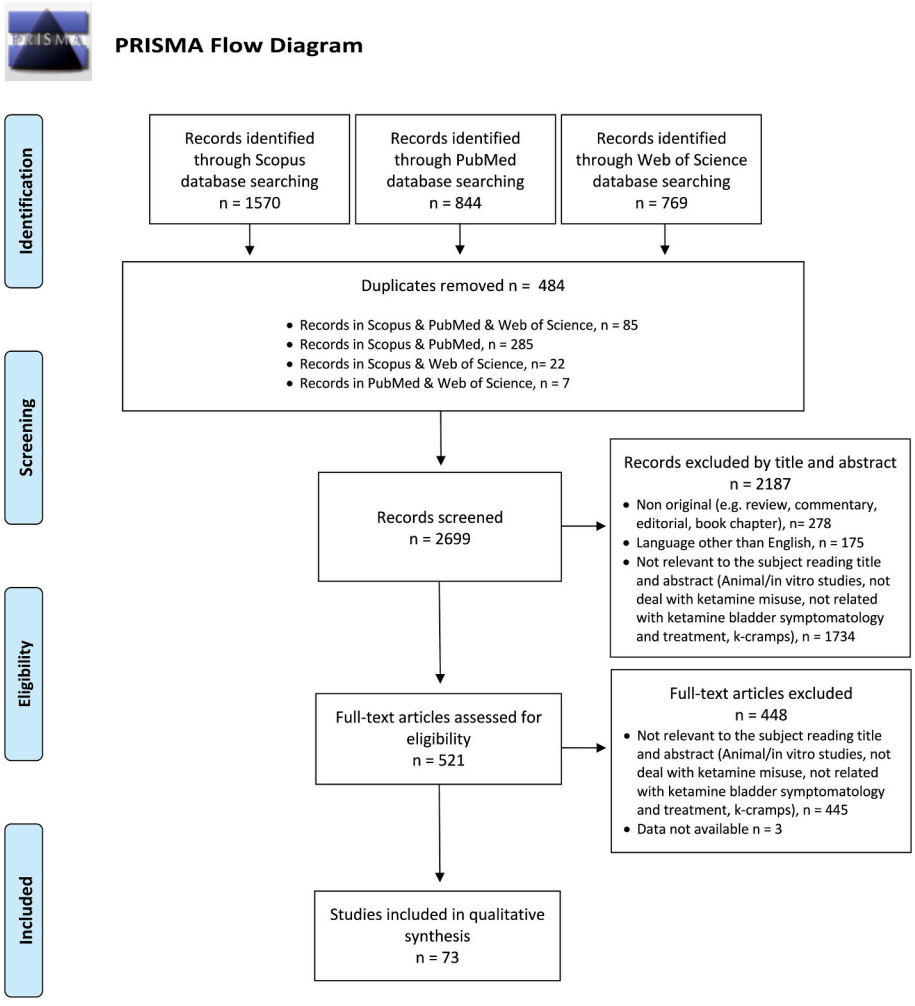

Fig. 1. PRISMA flow diagram of the methodology of the systematic literature review.

available literature.

3. Results

3.1. Study selection

The database search identified a total of 3183 records (PubMed = 844; Scopus = 1570; WoS = 769), and no additional records were identified from other sources. After removal of duplicates (n = 484), 2699 records were screened. Of these, 1734 were excluded based on title and abstract screening, 175 were excluded because they were not published in English, and 278 were non-original articles. The reviewers assessed 521 full-text articles for eligibility; 443 did not meet the inclusion criteria and 3 were unavailable. Ultimately, 73 studies were included in this systematic review (Fig. 1). The included studies comprised 38 case reports, 15 case series, 15 observational studies (cross-sectional, cohort, or survey-based), and 5 controlled studies (including randomized and non-randomized designs). The authors then organized these studies into thematic subsections according to the main clinical domains addressed.

3.2. Ketamine addiction

Out of a total of 73 studies included in the review, 56 specifically addressed ketamine dependence or addiction. Most of the available evidence consisted of single case reports or small case series, with only a limited number of observational cohorts and interventional studies. Most patients were young males, typically between 20 and 35 years old, although extreme ages ranging from adolescence to over 50 years were also reported.

Patterns of use were heterogeneous, with intranasal administration being the most frequently reported route, often involving escalating doses up to several grams per day. Chronic exposure ranged from a few months to more than a decade. Psychiatric comorbidities were commonly reported, including major depressive disorder, anxiety, bipolar disorder, and psychotic syndromes. Polysubstance use was frequently described, with ketamine particularly misused in combination with alcohol, cannabis, MDMA, cocaine, and benzodiazepines.

Treatment approaches varied widely. A symptomatic treatment/management approach, typically including benzodiazepine tapering; analgesics; and antidepressants was often adopted in acute settings. Pharmacological interventions included SSRIs for comorbid depression, naltrexone for craving reduction, lamotrigine and gabapentinoids for mood stabilization or craving, and antipsychotics for ketamine-induced psychosis. Psychotherapeutic interventions such as motivational interviewing, cognitive-behavioural therapy, occupational therapy models (e.g., Kawa framework), and relapse-prevention strategies were also reported. Several studies emphasized multidisciplinary approaches combining medical management, psychiatric care, and harm-reduction counselling. Clinical outcomes were mixed. After inpatient or outpatient interventions, some patients achieved sustained abstinence, while others relapsed, particularly in contexts of comorbid psychiatric disorders or polydrug use. Long-term follow-up data were scarce, limiting the possibility of drawing firm conclusions on the durability of treatment effects. Overall, the evidence may suggest that multimodal, individualized, and integrated approaches are essential to address the complex presentation of ketamine dependence. For detailed information please refer to Table 1.

3.3. Ketamine-induced bladder dysfunction (KBD)

Bladder complications emerged as one of the most consistent and severe medical consequences of chronic ketamine misuse. Across the included studies, patients were typically young males (mean ages ranging 20–30 years), although females were represented as well. Duration of exposure varied widely, from several months to over a decade, with most cases reporting daily intranasal use of several grams.

Clinical manifestations were characterized by irritative lower urinary tract symptoms (LUTS), including increased urinary frequency/urgency, nocturia, dysuria, haematuria, and suprapubic pain. Advanced cases frequently showed contracted bladder with markedly reduced functional capacity (<100–300 ml); bladder wall thickening; and cystoscopic findings of inflammation, neovascularization, and ulcerative lesions. Hydronephrosis, vesicoureteral reflux, ureteral strictures, and progression to obstructive nephropathy and renal impairment were frequently documented. Rare but severe complications included papillary necrosis, bladder diverticula, and, in one report, bladder leiomyosarcoma.

Therapeutic approaches were heterogeneous. First-line strategies often included symptomatic medical therapy such as: non-steroidal anti-inflammatory drugs, anticholinergics, β3-agonists, phenazopyridine, opioids and gabapentinoids. Intravesical treatments (hyaluronic acid, chondroitin sulfate, lidocaine, heparin, botulinum toxin A) were frequently trialled, with variable levels of benefit. Several reports described hydro-distension or bladder irrigation for symptomatic relief. In severe or refractory cases, surgical interventions such as augmentation entero-cystoplasty, bladder auto-augmentation (BATV), substitution cystoplasty, partial or subtotal cystectomy with neobladder formation, and long-term ureteral stenting or nephrostomy were required.

Overall, bladder outcomes were strongly correlated with duration and intensity of ketamine use. Symptom severity tended to improve with levels of abstinence being reported, but many patients with advanced disease required invasive procedures, and structural damage was often irreversible. Multidisciplinary management, involving urologists, nephrologists, and addiction specialists, appeared essential for optimal outcomes. For detailed information please refer to Table 2.

3.4. K-cramps

Recurrent abdominal and pelvic pain ("K-cramps") was frequently described among chronic ketamine users, typically young adults with prolonged exposure. Symptoms included colicky abdominal pain, suprapubic or flank discomfort, and post-prandial worsening, often severe enough to prompt Emergency Department visits.

Management was mainly supportive (hydration, dietary adjustments, hot baths), with pharmacological options such as NSAIDs, acetaminophen, opioids, and anticholinergics having been reported. In cases associated with severe uropathy, clinicians performed surgical interventions such as augmentation enterocystoplasty.

Across studies, abstinence from ketamine consistently led to symptom resolution, whereas ongoing use was linked to persistence or recurrence. K-cramps, therefore, appeared to represent a distinct but under-recognized manifestation of ketamine misuse, with early recognition and cessation being crucial for recovery. These findings are presented in Table 3.

3.5. Recommendations for clinicians

The current review of clinical reports and observational studies identified a range of clinical considerations for the management of patients with ketamine misuse and related complications (see Table 4). These considerations span multiple domains, including addictive behaviours, psychiatric symptoms, and physical complications such as urological and gastrointestinal manifestations. The reported recommendations are derived from a narrative synthesis of heterogeneous evidence, primarily consisting of case reports, case series, and observational studies. As such, they do not represent formal clinical guidelines or evidence-graded recommendations, but rather reflect recurring clinical patterns, individual study findings, and author-level interpretation of the available literature. The strength and level of supporting evidence vary considerably and should be interpreted with caution.

Table 1
Clinical studies and case reports on ketamine abuse and dependence.

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Avra et al. 2024	Case report	Inhalational 0.5–1 g/day for 3 y plus IM/IV 1–3 g/day for 8 mo (chronic heavy use)	1 (M 1/F 0)	31 y	Major depressive disorder; chronic back pain	NR	≈3 y + 8 mo	Self-discontinuation; residential SUD treatment Cessation of ketamine use	NR	Symptomatic analgesia; harm-reduction counselling	Recurrent severe abdominal/back pain ("K cramps") Atraumatic back pain; chest tightness; dyspepsia
Bhad et al., 2016	Case report	IM ketamine 50–200 mg per dose daily; 4 y dependence (veterinary professional)	1 (M 1/F 0)	48 y	Alcohol (past) & nicotine dependence (current)	Alcohol; tobacco	4 y	Naltrexone 50 mg/ day; motivational therapy; relaxation exercise, relapse prevention	Ketamine dependence; withdrawal symptoms Derealization, "k-hole", visual hallucinations, a sense of slowing of time	Naltrexone; motivational enhancement	NR
Boccio et al., 2025	Case report	IV/IM ketamine 500–1000 mg/ week for 3 y (recreational)	1 (M 0/F 1)	25 y	Anxiety, OCD	NR	3 y	Symptomatic ED care; addiction referral	Acute anxiety	IV lorazepam	Crampy abdominal pain, nausea/vomiting
Caloro et al., 2018	Case report	Poly-NMDA antagonist abuse (ketamine, MXE, methoxphenidine, PCP) 14 y	1 (M 1/F 0)	32 y	Substance-induced psychotic disorder	Cannabinoids; dextromethorphan; alcohol; NMDA analogues	14 y	Valproate; aripiprazole; psychotherapy	Paranoid delusions and auditory hallucinations; dissociative symptoms aggression;	Valproate; antipsychotic (aripiprazole)	Legal issues; near-death experiences
Chao & Shai, 2010	Case report	Daily snorting for 3 y; forced cessation	1 (M 0/F 1)	19 y	Major depression	NR	3 y	Forced cessation; duloxetine 60 mg/ day	Major depression Depressive mood, insomnia, poor appetite, self-destructive behavior, worthless feeling with suicidal ideation	Duloxetine 60 mg/day	NR
Chan, 2012	Retrospective toxicology case-series (Hong Kong PIC)	Acute vs chronic insufflation; chronic mean 8.6 y use (median 4 y)	284 cases (NR/NR)	Mostly 10–39 y	NR	NR	8.6 y (chronic)	Supportive care; cessation advice	10% acute psychosis/ confusion	Symptomatic	Chronic abdominal pain 66%; hypertension/ tachycardia 27%
Chang, Huang et al., 2016	Case report	Snorting 6 g/day for 8 y; increased to 10 g/day; dependence	1 (M 1/F 0)	38 y	NR	NR	8 y heavy use	Substance treatment ward; sertraline 100 mg/d; benzodiazepines	Major depressive disorder	Sertraline 100 mg/d	Abdominal cramps; urinary frequency
Chang et al., 2012	Case series	Mean daily 3.2 g; abuse 2–36 mo; LUTS onset at 12.7 mo	20 (M 13/F 7)	Mean 25.8 y (Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Svendsen et al., 1999;	NR	NR	Mean 12.7 mo	Cessation counselling; 10 quit; medical & endoscopic management	NR	NR	Abnormal LFT (50%), jaundice (5%)

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
				Zhuo, 2002)							
Chen et al., 2012	Case report	Weekly intranasal use for 3 y dose NR	1 (M 1/F 0)	18 y	NR	None	3 y	Ketamine cessation only	NR	NR	Suprapubic pain
Chen & Huang, 2016	Case report	Intermittent recreational ketamine and nitrous oxide for ~2 y; doses NR	1 (M 0/F 1)	20 y	NR	Chronic nitrous oxide inhalation	2 y intermittent	Cessation advised	NR	NR	Subacute combined degeneration; dystonia; pseudoathetosis; polyneuropathy
Chen et al., 2020	Cross-sectional inpatient study	Mean duration 8 y; snorting; avg. 3.8 g/day; 24.8 d/mo before admission	104 (76 M/ F 28)	Mean 30.3 y ± 6.1	22.1% current MDD; 59% moderate-severe depression; 39% moderate-severe anxiety	None (other substances excluded)	Mean 8 y	Inpatient withdrawal (diazepam taper); SSRIs for MDD	Depression, anxiety, high craving	Diazepam (5 mg); SSRIs (7 pts)	NR
Chen et al., 2022	Case report	IV ketamine injection; dose NR; urine screen positive	1 (M 1/F 0)	40 y	NR	Alcohol abuse; benzodiazepines	NR	NR	NR	NR	Gangrenous cellulitis; CoNS bacteremia; pneumonia; necrosis
Chen et al., 2013	Case report	Nasal insufflation 2–5 g/day for ~4 y; relapsed after 1 y abstinence; resumed 2 mo before presentation	1 (M 0/F 1)	20 y	NR	None reported	~4 y	Anticoagulation (LMWH→warfarin); cessation counselling	NR	NR	Left renal infarction due to vasospasm
Cheung et al., 2014	Cross-sectional pilot study	23 female inhalational users with LUTS; mean use 55.6 mo; abstinent 7.9 mo	23 (M 0/F 23)	Mean 20.6 y (SD 3.7)	NR	NR	Mean 4.6 y	NR	NR	NR	Elevated urinary EGF suggesting bladder inflammation
Chung et al., 2014	Surgical case series	Chronic abuse mean 3.82 y; contracted bladder 50 ml	14 (M 4/F 10)	Mean 26.7 y	NR	NR	Mean 3.82 y	Augmentation enterocystoplasty ± ureteric reimplant; counselling	NR	NR	UTIs; renal impairment; sepsis
Critchlow, 2006	Case report	Daily snorting 1–7 g/day for 6 y	1 (M 1/F 0)	25 y	NR	Alcohol to ease withdrawal	6 y	Motivational interviewing; diazepam taper 20 mg over 3 d; multivitamins and thiamine	Craving; anxiety; withdrawal symptoms	Diazepam taper	Perforated nasal septum; abdominal pain; anorexia with weight loss
Giannini et al., 2000	Double-blind randomized pilot study	Acute unintended ingestion; single recreational dose (quantity NR); subjects initially presumed PCP intoxicated	21 (M 21/F 0)	22–30 y	NR	None detected (toxicology negative for other substances)	Single acute episode	5 mg IM haloperidol (vs active placebo)	Acute dissociative; paranoid psychosis, agitation	Haloperidol 5 mg IM	Tachycardia, flushed dry skin; nystagmus
Goyal et al., 2014	Case report	IM ketamine escalating 50–2500 mg/day; cyclical	1 (M 1/F 0)	30 y	Dysphoria, sleep disturbance	Alprazolam, pentazocine, midazolam, nicotine, alcohol	3 y	Inpatient detox; motivational interviewing;	Craving; dysphoria; depersonalization	Motivational interviewing; naltrexone	Injection site fibrosis & ulcers; occupational impairment

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
		dependence over 3 y						naltrexone 50 mg/ day			
Hamza and Bryson, 2011	Cross-sectional descriptive survey (recovered anesthesia providers)	7/30 had ketamine addiction (IV/ intranasal); duration NR	30 (M/F NR)	NR	Dysphoria, relapse-related distress	Opioids, benzodiazepines, propofol common	NR	Inpatient rehabilitation; 12-step programs and/ or monitoring contracts	Dysphoria after re-exposure, craving, emotional distress	12-step programs, journaling, drug testing, full provider disclosure	Relapse risk when medically re-exposed to triggering agents
Hoskins, 2009	Case report	Intranasal 6 g/day for 5 y	1 (M 1/F 0)	20 y	NR	NR	5 y	NR	NR	NR	Social isolation; poor sleep; occupational impairment
Hsiao et al., 2024	Quasi-experimental study (Kawa model vs psychoeducation)	Mandated SUD clients; primary ketamine or amphetamine use; dosage NR	97 (M 80/F 17)	Mean 32 y (SD 9.6)	Variable anxiety/ depression levels	Amphetamines common; poly-drug	NR	Kawa-model group therapy (4 session for 2 h/week) vs 8 h of lecture-based psychoeducation; mandated abstinence	Craving; reduced quality of life (physical, psychological, social, environmental domains)	Kawa model therapy (occupational therapy)	NR
Huang et al., 2008	Case report	IV ketamine 2–3×/ week for ~6 mo; symptoms within several days of starting use	1 (M 1/F 0)	25 y	NR	Smoking 0.5 pack/ day	~6 mo	Cessation counselling;	NR	NR	Severe LUTS; eosinophilia
Huang et al., 2016	Case report	Smoking then snorting 4–5 g/day (6–10 uses/day) for 3 y; ongoing cravings	1 (M 1/F 0)	25 y	Mood dysregulation (suspected); anxiety on withdrawal	NR	3 y	Lamotrigine 100 mg/ day; inpatient detox	Craving; anxiety; dysphoria	Lamotrigine (anti-craving)	Dizziness, nausea, headache, asthenia after attempting to use ketamine under lamotrigine treatment
Hung et al., 2019	Quasi-experimental comparative study (prospective controlled educational intervention)	Mandated ketamine users identified by police; mode and dose NR	395 (M 344/F 51)	Mean 27 y (SD 5.6)	NR	NR	Age of first ketamine use reported ~14 y	IMB (information, motivation and behavior skills) vs EAU (education-as-usual) drug-education programs	NR	NR	NR
Hung et al., 2023	Prospective cohort study (GBMSM chemsex)	Chemsex patients; 8.6% reported ketamine use during sessions; frequency and dose NR	152 (M 152/F 0)	Median 28 y (IQR 25–34)	32.1% moderate-high anxiety/ depression	High poly-drug use (methamphetamine 48%, GHB 22%, MDMA 13%, etc.)	NR	HERO (Healing, Empowerment, Recovery of Chemsex) harm-reduction program: chemsex care plan, mental-health clinic, recovery groups	Anxiety & depression symptoms	Mental-health clinic visits; recovery groups; group therapy (mindfulness-based relapse prevention, self-exploration, self-regulated learning)	HIV (25.7% of participants); STI risk; poly-drug harms
Jalil & Gupta, 2012	Case series	Street ketamine inhalation up to 4 g/day in one case; variable duration	4 (M 2/F 2)	20–46 y	NR	NR	Variable	Primary recommendation: complete abstinence from ketamine; symptomatic bladder management; early urology referral.	NR	NR	Squamous metaplasia (premalignant)
Jhang et al., 2017	Retrospective comparative study	Chronic ketamine abuse; mean 4.5 y;	53 (M 25/F 28)	Mean 28 y (18–43)	NR	NR	Mean 4.5 y	All advised permanent cessation of ketamine	NR	NR	Urinary urgency incontinence; dysuria; recurrent UTIs; acute pyelonephritis

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Kyaw et al., 2024	Case report	Prior ketamine abuse (details NR); suspected chronic use	1 (M 1/F 0)	30 y	NR	NR	NR	NR	NR	NR	Fever; productive cough; pleuritic chest pain; dyspnea; CT: multifocal cavitary pneumonia with bilateral parapneumonic effusions (*Pantoea septica* bacteremia)
Lamers et al., 2022	Case report	Intranasal; 7 g/ week escalating to 20–30 g/week over 6 months	1 (M 1/F 0)	18 y	ADHD	NR	≈ 6 months	Advice to cease ketamine; counselling	NR	NR	AKI; pyuria; microscopic and gross haematuria; severe bilateral flank pain
Lee et al., 2005	Case series (5 young adults with type 1 diabetes)	Oral ketamine + ecstasy and alcohol at rave; acute episodes	5 (M 5/F 0)	19–22 y	One case with depression and schizophrenia	Polysubstance (ecstasy, heroin, marijuana, alcohol)	Occasional binges	Harm-reduction counselling	Agitation, anxiety, insomnia, and panic attacks in one case	Methadone, diazepam; ongoing psychiatric medications (antipsychotics, antidepressants, benzodiazepines) in one patient	DKA; hyperosmolar hyperglycemic state; recurrent hypoglycaemia; fatty liver; gastroparesis; vomiting; confusion
Lee, Baik et al., 2024	Narrative review (78 reported cases + local illustrative case report)	Chronic street ketamine (powder smoked/snorted, oral ingestion); months–years	78 (M 48/F 30); local illustrative: single young male	Mean 25 y	NR	Marijuana/tobacco mixture; sometimes combined with ecstasy, alcohol	Months-years	Immediate cessation recommended; counselling referral for addiction; multidisciplinary approach	Acute dissociation; hallucinations; amnesia; delirium; agitation; stereotypies; memory deficits; learning and attention impairments; withdrawal possible	Detoxification and counselling for dependence	Tachycardia; hypertension; respiratory depression; blurred vision; increased body temperature; flashbacks; impaired coordination
Lee & Busiol, 2015	Case series	Snorting 1–10 g/ day; duration 2–15 y	9 (M 4/F 5)	Mean 31 y (25–42)	NR	NR	2–15 y (mean ~ 8 y)	Cessation counselling	NR	NR	Flank pain; fever in acute pyelonephritis; elevated serum creatinine; ureteral wall inflammatory polyps
Lee, Chopra et al., 2024	Case series	Smoking 0.1–6 g/ day for 5 y (F); intranasal 1–2 g/ day for 1 y (M)	2 (M 1/F 1)	28–35 y	Case 1: schizoaffective disorder; case 2: depression; GAD; AUD	Alcohol (case 2); none others	Case 1: 5 y of escalating use	Gabapentin up to 1.2 g/day + topiramate up to 100 mg/day	Depression; anxiety; dissociation; amotivation; anhedonia	Gabapentin; topiramate	Bilateral finger paresthesias from topiramate (dose-related, resolved with dose reduction); daytime somnolence from gabapentin (resolved with dose adjustment)
Liao et al., 2019	Cross-sectional survey	106 rehabilitation clients; 92.9% daily use; snort 34%, smoke 33%, both 33%; <10 g/ day; mainly used several times per day; mean 75 mo use	106 (M 95/ F 11)	Mean 24.9 y (SD 6.4)	NR	80% polysubstance abuse (MDMA, marijuana, amphetamine, opioids etc.)	Mean 75 mo (~6 y)	Rehabilitation program	NR	NR	NR

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Liao et al., 2018	Case report	Intranasal inhalation; initially once weekly, escalating to once every 2–3 days, up to ~10 g/day	1 (M 1/F 0)	29 y	NR	NR	3 y	Ketamine cessation advice	NR	NR	Median-lobe BPH
Lim, 2003	Case series	Insufflation up to 4 g/day for 4–5 months	2 (M 2/F 0)	32–35 y	Behavioral addictions (gambling, compulsive sexual activity)	Polysubstance (alcohol, benzodiazepines, cannabis, MDMA, heroin)	4–5 mo	Inpatient detox; benzodiazepines; haloperidol; naltrexone; propranolol; residential rehabilitation	Multimodal hallucinations (auditory, visual, olfactory, tactile); paranoid ideation, dissociation/ depersonalisation; withdrawal symptoms (chills, lacrimation, nightmares, craving)	Benzodiazepines; haloperidol	Epistaxis from constant snorting; anosmia from chronic intranasal use
Lin, Lin et al., 2016	Case report	Inhalation 0.2–3 g/ day for 12 y	1 (M 1/F 0)	28 y	none	None	12 y	Abstinence; inpatient withdrawal	Withdrawal depression & anxiety	None (spontaneous remission)	Fatigue, insomnia, yawning, and a dysphoric mood
Lin, Lane et al., 2016	Case report	Intranasal daily for 5y, 1–3 g/day in the last 4–5 months	1 (M 1/F 0)	34 y	Bipolar I disorder; substance dependence	Marijuana daily; past alcohol/ cocaine/meth/LSD/ MDMA	5 y	Inpatient cessation; lithium; lamotrigine; olanzapine	Acute agitation with referential ideation and paranoia; suicidal ideation	Benzodiazepines; risperidone short-term	NR
Lin, Lane et al., 2016	Cross-sectional case-control, urinary proteomics + targeted metabolite analysis	Chronic recreational self-administration of ketamine (mean 4.0 ± 2.2 g/day; last use ≈ 6 ± 6 days before sampling)	56 KA (41 M, 15 F)‖40 HC (25 M, 15 F)	≈31.3 ± 6.3 y (KA)	Major psychiatric disorders excluded; others not reported	Other substance-use disorders excluded	All ketamine abusers met DSM-IV-TR criteria for ketamine dependence confirmed by two board-certified psychiatrists; chronic self-administration (mean 4.0 ± 2.2 g per day during the 90 days before admission; last use ≈ 6 ± 6 days before sampling; 85% consumed >2 g/day)	In-patient admission to an addiction centre for medically-supervised ketamine detoxification; no specific pharmacotherapies beyond standard detox care are detailed	NR	NR	Urinary inflammation; elevated APOA1; pain rating scale >50 mm in 35%
Lu et al., 2016	Case report	Inhalation initially 5 and then 10–15 g/week for 12 mo	1 (M 1/F 0)	26 y	Tourette syndrome; OCD	NR	4 y	Abstinence; inpatient observation	Euphoria, labile mood, dissociation, and auditory hallucinations in the first hours; Mania then depression with worsening of obsessive–compulsive	Sertraline 200 mg/d; Aripiprazole 10 mg/d	NR

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
									symptoms after withdrawal		
Man, 2020	Randomized controlled trial	Ketamine use ≥2×/month for ≥6 months within last 2 years; abstinent during study	90 (M 90/F 0)	Mean 24 y (Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Jiang et al., 2014; Juneja et al., 2024; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Page et al., 2021; Reijerkerk et al., 2010; Roncero et al., 2025; Shahani et al., 2007; Svendsen et al., 1999; Tang et al., 2014; Verma et al., 2025; Zhuo, 2002)	NR	None (poly-drug users excluded)	Mean ~ 6 y (75 mo)	VR-based vocational cognitive training (VRG) vs tutor-administered (TAG) vs wait-list control	NR	NR	Baseline cognitive deficits; attention & memory improved post-VR
Manongi et al., 2022	Case report	Recreational ketamine ≥10 y; dose/route NR	1 (M 0/F 1)	29 y	NR	NR	10 y	Counselling; advised abstinence	NR	NR	Cholangiopathy; AKI; hyponatremia
Marongiu et al., 2025	Case series	Recreational intranasal/ combined use; doses NR; acute ED presentations	3 (M 1/F 2)	22–36 y	Depression, suicidality (1/3 pts)	Alcohol, oxazepam, MDMA, cocaine	NR	Observation, catheterization, oxybutynin; psychiatric referral	NR	Psychiatric referral	Agitation, apneas, vomiting, double vision and instability
Marongiu et al., 2025	Retrospective cohort (38,350 TX treatment admissions)	Club-drug clients 1988–2003; ketamine among ecstasy, GHB, meth, Rohypnol; high polysubstance	38,350 (≈ 54% M)	Ecstasy admits ≈ 21.8 y; meth ≈ 29.9 y	22% DSM depression; conduct disorder in youth; psychotropic meds rising	89% ≥ 2 substances; marijuana, alcohol, meth prevalent	Mean lag first-use→treatment 7–11 y	Detox, residential, outpatient; completion 25–52%	Depression, conduct disorder, anxiety	11–21% received antidepressant/ antianxiety	NR
Meng et al., 2015	Pilot case series	Intravesical hyaluronic acid for ketamine cystitis;	5 (M 1/F 4)	Mean 22 y (SD 1.5)	NR	NR	Mean 5.7 y (68 mo)	Cessation advice; weekly HA 40 mg × 6 then monthly × 3	NR	NR	NR

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
		failed oral meds; mean abuse 68 mo									
Misra et al., 2014	Retrospective cohort	Inhalational ketamine 1/ week–5 g/day; duration 1–10 y	34 (M 27/F 7)	Median 23 y (17–45)	Depression 15%; personality disorder 3%	35% polydrug (cocaine, heroin, cannabis, ecstasy, alcohol)	1–10 y	Cessation advice; analgesics, antimuscarinics, antibiotics; hydrodistention; cystectomy (Guerrini et al., 2025)	NR	NR	HIV 18%; renal impairment 3%
Ng et al., 2013	Retrospective case series	Chronic ketamine abuse 3–15 y; all resumed use post-surgery	4 (M 1/F 3)	21–30 y (mean 27)	NR	NR	3–15 y	Anti-inflammatory agents, antimuscarinic agents and analgesics, with no significant clinical improvement, then augmentation ileocystoplasty	NR	NR	Ureteric strictures; renal impairment; sepsis
Okunlola et al., 2024	Case report	Chronic intranasal use; 3 g sniffed 3 days before admission; > 1 year of abuse	1 (M 1, F 0)	24 y	Anxiety, depression (history)	NR	> 1 year of chronic ketamine misuse	Withdrawal counselling; multidisciplinary inpatient admission	Pre-existing anxiety/ depression (no new acute episode)	NR	Cachectic, reduced liver function, anemia, AKI, metabolic acidosis, cholestasis, gastric dilatation, systolic heart failure, sepsis
Peng et al., 2016	Case report	≈5 g/day for 1 y; stopped >1 y before augmentation enterocystoplasty; route NR	1 (M 0/F 1)	28 y	NR	NR	1 y	Intravesical hyaluronic acid × 1; augmentation enterocystoplasty	NR	NR	Acute pyelonephritis, recurrent UTIs; successful pregnancy & vaginal delivery 18 mo post-AE
Rahman et al. 2024	Case report	5 g/day for 2 years, stopped 7 years ago	1 (M 0, F 1)	34 y	NR	NR	Heavy daily ketamine use for 2 years	Sustained abstinence; nephrology & psychological follow-up	NR	NR	Stage 3 CKD, nausea, sepsis, prior elevated LFTs
Roxas et al., 2021	Case report	Monthly IV + oral lozenges 100 mg 4×/day for 8 mo	1 (M 1/F 0)	35 y	PTSD, bipolar II, BPD	Cannabis (daily vaping),alcohol in full sustained remission	8 mo	Cessation inpatient; lorazepam, olanzapine, valproate	Worsening depression and suicidal ideation, severe agitation, dysphoria during withdrawal	Benzodiazepines; antipsychotics; mood stabilizer	NR
Schifano et al., 2021	Pharmacovigilance database analysis	Medicinal ketamine (IV, nasal, oral); 1–7500 mg; 1 day–>1 y exposure	1758 (F 1157/M 561/not specified)	Adults 18–64 y (most)	NR	19.6% concomitant drugs (gabapentin, opioids)	Variable; many 1 mo–1 y	Ketamine withdrawn/reduced in ADR cases	NR	NR	4.5% fatalities; hospitalisation 68%
Selby et al., 2008	Case report	Regular intranasal snorting for 2 years; last use days before admission	1 (M 1/F 0)	26 y	NR	Cannabinoids; lignocaine	2 y	Supportive ICU care; cessation counselling	NR	NR	Acute renal failure; cholangiopathy; sepsis; pancreatitis
Shahzad et al., 2012	Case report	Oral analgesic ketamine 60 mg QDS (240 mg/day)	1 (M 1/F 0)	52 y	NR	Chronic pain opioids & adjuvants	3 y	Ketamine cessation; nerve-sparing cystoprostatectomy with ileal conduit	NR	NR	Deranged liver tests

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
		for chronic pain; 3 y use									
Sharma et al., 2024	Case report	Chronic recreational use 8 y; route NR; dosage NR	1 (M 0/F 1)	29 y	NR	None reported	8 y	Ketamine cessation advised; ERCP with sphincterotomy	NR	NR	Sphincter of Oddi dysfunction; dilated CBD; elevated liver enzymes
Smart, Kabir et al., 2013	Case report	Chronic intranasal ketamine; 1–2 g/ day for 2–3 y then 2 g 2–3×/week; 10 y total; abstinent 4–5 month	1 (M 1/F 0)	30 y	NR	NR	10 y	Self-cessation	NR	NR	NR
Sturgess et al. 2023	Retrospective cohort	Recreational ketamine users with KIU; dose NR; 2011–2022 cohort	81 (M 59/F 22)	Median 30 y (IQR 27–34)	30.9% mental-health diagnoses	NR	NR	NR	Anxiety/depression in 30.9%	NR	Hepatic failure from cholangiopathy; sepsis with renal abscess
Tam et al., 2014	Cross-sectional study in prospective cohort	Mean 18.5 g/week; duration 81 mo; active 214 vs ex-abusers 104	318 (M 144/F 174)	Mean 24.4 ± 3.1 y (Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Jiang et al., 2014; Juneja et al., 2024; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Page et al., 2021; Reijerkerk et al., 2010; Roncero et al., 2025; Svendsen et al., 1999; Tang et al., 2014; Verma et al., 2025; Zhuo, 2002)	NR	50.3% polysubstance	6.8 y	NR	NR	NR	NR
Tan et al., 2021	Retrospective cohort study	NR	53 (M 40/F 13)	Mean 25 y (13–38)	NR	NR	Mean 3 y	NR	NR	NR	Mild complications of surgery (UTI, hematuria); no systemic issues

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Tam et al., 2014	Cross-sectional clinical study	At least ≥ 2 uses/ month for ≥6 mo; mean duration 6.9 y;	84 (M 45/F 39)	Mean 24.5 y (SD 4.0)	60% depressive; 37% anxiety symptoms	72% polydrug; mean 1.3 other substances	Mean 6.9 y	NR	Depressive, anxiety, mild psychotic Sx	NR	NR
Tran et al., 2014	Case report	Ketamine 3–5×/ day for 4 y; heavy abuse;	1 (M 1/ F 0)	24 y	NR	Cocaine; intravenous drugs	4 y	NR	NR	NR	Bilateral hydroureteronephrosis; Elevated creatinine; mild ataxia
Tsai et al., 2020	Case report	NR	1 male	29 y	NR	polysubstance abuse (details NR)	6 mo	NR	Mania; agitation	NR	Myalgia dark urine Severe rhabdomyolysis (CK > 300 kU/l); dyspnea; Acute kidney injury (AKI); full renal recovery
Tung et al., 2014	Cross-sectional psychometric validation	Treatment-seeking intranasal users; median 10.5 g/ week; 56% daily	80 (M 49/F 31)	Median 27 y (18–57)	NR	High lifetime MDMA, cannabis, cocaine use	Median 4.5 y	SDS-K validation in treatment clinics	NR	NR	NR
Unterrainer et al., 2014	Case report	Ketamine; 1–2 g/ day for 2–3 y then 2 g 2–3×/week; 18 mo heavy use;	1 male	19 y	Depression, with anhedonia and suicidal ideation	Valium, magic mushrooms, cannabis	18 mo heavy use	Self discontinuation since one month ago	Depression, anxiety, anedhonia anergy Paranoid ideation Thought disorder	EEG neurofeedback + short-term psychodynamic psychotherapy	Irritable Bowel Syndrome
Weiner et al., 2000	Prospective observational study (case series)	11 patient Injection subcutaneously or i.m.100–200 mg; 9 patient inhalation	20 (M 11/F 9)	15–40 y	NR	1 patient LSD. Another 1 methamphetamine	Acute episodes	Supportive care; benzodiazepines; IV fluids; charcoal for those who had oral ingestion	8 patients had anxiety; 6 had altered mental status 3 had hallucinations; five patients report agitation	Benzodiazepines	Half patient had tachycardia; 3 patients had rotatory nystagmus; 3 had midriasis 1 with chest pain + hypertension; 2 had mild rhabdomyolysis
Wang et al., 2016	Prospective nonrandomized controlled study	Ketamine primary drug (~53%); polysubstance common	121 (M 92/ F 29)	Mean 16.1 y (SD 1.1)	NR	Methamphetamine, MDMA common	NR	10-session motivational enhancement psychotherapy ± parenting skill training	NR	NR	NR
Wang, Chen, Lin, Chen et al., 2018	Prospective longitudinal cohort	NR	92 (M 71/F 21)	Mean 16 y (Chiappini et al., 2023; Juneja et al., 2024; Page et al., 2021; Short et al., 2018; Verma et al., 2025)	NR	NR	NR	10-week family-oriented motivational & parental skill training	NR	NR	NR
Wong et al., 2013	Case report	Ketamine insufflation	1 (M 1/F 0)	26 y	NR	NR	>4 y chronic use	Intravenous fluid replacement and supplemental oxygen.	NR	NR	Pneumomediastinum; surgical emphysema; pneumorrhachis; Acute on chronic renal failure; liver impairment;

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Yang et al., 2020	Case series	0.1–3 g 2–19×/ week	18 (M 18/F 0)	Mean 24.5 y (Chang et al., 2012; Chu et al., 2008; Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Jiang et al., 2014; Juneja et al., 2024; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Reijerkerk et al., 2010; Roncero et al., 2025; Shahani et al., 2007; Svendsen et al., 1999; Tang et al., 2014; Tsai et al., 2009; Zhuo, 2002)	NR	NR	2.1–4 y	Self discontinuation	NR	NR	metabolic acidosis; Chronic hydronephrosis 5 patients with an increased creatinine level and 4 with a decreased GFR and an elevated creatinine level
Yee et al., 2015	Prospective case series	Mean 15.7 g/week; 70% ≥7 uses x/week; 15% 1–3 uses x/ week; 10% 4–6 uses x/week; 4.6% uses <1 uses per week.	319 (205/ 258)	Mean 25 y ± 3.8	NR	NR	Mean 6.9 y	Motivational interviewing & social-worker support	NR	NR	NR
Zeng et al., 2017	Prospective case series	NR	36 (M 30/F 6)	Mean 26 y (19–38)	NR	NR	1–5 y	NR	NR	NR	Two patient whit positive urine bacterial culture. Elevated AST and ALT in 5 patients. Hematuria in 3 patients. Suprapubic pain in 11 patient.

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Table 1 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Psychiatric comorbidity	Poly-abuse (substance)	Abuse/ dependence	Abuse/dependence treatment	Psychiatric symptoms	Psychiatric symptoms Treatment	Other symptoms
Zhong et al., 2015	Case report	Intranasal ketamine abuse; 5 y; dose	1 (M 1/F 0)	31 y	NR	NR	5 y	Cessation program (no details are reported)	NR	NR	Hemorrhagic shock
Zuccoli et al., 2014	Case report	Chronic oral ketamine; weekly intake escalating to >4 ×/week for 3 months	1 (M 1/F 0)	34 y	None	Alcohol abuse; cannabis; occasional cocaine	3 mo	Inpatient benzodiazepines	Ketamine-induced psychosis (anxiety-agitation, delusions bizarre behavior)	Paliperidone 6 mg then 3 mg; benzodiazepines	Mild liver enzyme elevation; tachycardia, hypertension

M = male; F = female; SD = standard deviation; SUD = substance use disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; AUD = alcohol use disorder; GAD = generalized anxiety disorder; PTSD = post-traumatic stress disorder; BPD = borderline personality disorder; LUTS = lower urinary tract symptoms; UTI = urinary tract infection; CKD = chronic kidney disease; AKI = acute kidney injury; CBD = common bile duct; ED = emergency department; IM = intramuscular; IV = intravenous; NR = not reported; HA = hyaluronic acid; LMWH = low molecular weight heparin; ERCP = endoscopic retrograde cholangiopancreatography; DKA = diabetic ketoacidosis; HHS = hyperosmolar hyperglycemic state; CK = creatine kinase; CoNS = coagulase-negative Staphylococcus; SDSK = Severity of Dependence Scale for Ketamine; IMB = Information-Motivation-Behavior program; EAU = education-as-usual; VR = virtual reality; KA = ketamine abusers; HC = healthy controls; RCT, randomized controlled trial; CBT, cognitive behavioural therapy.

Table 2
Clinical studies and case reports on ketamine-associated bladder dysfunction, summarizing patterns of use, clinical manifestations, and therapeutic interventions.

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine bladder	Ketamine bladder treatment
Bhad et al., 2016	Case report	IM ketamine 50–200 mg per dose daily; 4 y dependence (veterinary professional)	1 (M 1/F 0)	48 y	4 y	Irritative LUTS (burning micturition, frequency, lower abdominal pain)	Urology consult; none specified
Boccio et al., 2025	Case report	IV/IM ketamine 500–1000 mg/week for 3 y (recreational)	1 (M 0/F 1)	25 y	3 y	Non-structural; dysuria ("K-cramps")	Supportive (fluids, antiemetics)
Chao & Shai, 2010	Case report	Daily snorting for 3 y; forced cessation	1 (M 0/F 1)	19 y	3 y	Severe LUTS (80 voids/ day) with urgency, painful hematuria; small thick-walled bladder	NR
Yiu-Cheung, 2012	Retrospective toxicology case-series (Hong Kong PIC)	Acute vs chronic insufflation; chronic mean 8.6 y use (median 4 y)	284 cases (NR/NR)	Mostly 10–39 y	8.6 y (chronic)	92% chronic cases with ketamine cystitis with dysuria; 32% acute LUTS	None
Chang et al., 2012	Case series	Mean daily 3.2 g; abuse 2–36 mo; LUTS onset at 12.7 mo	20 (M 13/F 7)	Mean 25.8 y (Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Svendsen et al., 1999; Zhuo, 2002)	Mean 12.7 mo	Severe LUTS; bladder capacity 70 ml; 8 hydronephrosis; cystoscopic neovascularization	Hydrodistention; pentosan + prednisolone; intravesical lidocaine/ heparin; hyaluronic acid; D-J stents
Chen & Wang, 2012a	Case report	Weekly intranasal use for 3 y dose NR	1 (M 1/F 0)	18 y	3 y	Contracted bladder; inflammatory mucosa with neovascularization petechial hemorrhages	None
Chen et al., 2013	Case report	Nasal insufflation 2–5 g/day for ~4 y; relapsed after 1 y abstinence; resumed 2 mo before presentation	1 (M 0/F 1)	20 y	~4 y	Hydroureteronephrosis; bladder petechial hemorrhage and multiple erythematous patches; contracted bladder (ketamine cystitis)	Bladder hydrodistention (diagnostic)
Cheung et al., 2014	Cross-sectional pilot study	23 female inhalational users with LUTS; mean use 55.6 mo; abstinent 7.9 mo	23 (M 0/F 23)	Mean 20.6 y (SD 3.7)	Mean 4.6 y	Irritative LUTS; normal bladder capacity	None
Chung et al., 2014	Surgical case series	Chronic abuse mean 3.82 y; contracted bladder 50 ml	14 (M 4/F 10)	Mean 26.7 y	Mean 3.82 y	Contracted bladder; hydronephrosis 64.3%; VUR 57.1%	Ileal augmentation; ureteric reimplantation
Hoskins, 2009	Case report	Intranasal 6 g/day for 5 y	1 (M 1/F 0)	20 y	5 y	Severe lower urinary tract symptoms (LUTS); severe ketamine cystitis; small bladder capacity; hematuria	Antibiotics; planned cystectomy
Ho et al., 2010	Case report	IV ketamine 2–3×/ week for ~6 mo; symptoms within several days of starting use	1 (M 1/F 0)	25 y	~6 mo	Ulcerative cystitis; contracted bladder; bilateral hydronephrosis; narrowed cystoureteral junctions	Conservative; eventual dialysis
Huang et al., 2016	Case report	Smoking then snorting 4–5 g/day (6–10 uses/day) for 3 y; ongoing cravings	1 (M 1/F 0)	25 y	3 y	Irritative LUTS; ketamine cystitis	Symptomatic (no-specific)
Jalil & Gupta, 2012	Case series	Street ketamine inhalation up to 4 g/ day in one case; variable duration	4 (M 2/F 2)	20–46 y	Variable	Ulcerative cystitis; small bladder capacity (<150 ml); dysuria, frequency, suprapubic discomfort; intermittent haematuria	Symptomatic management: pentosan polysulfate, intravesical sodium hyaluronate, antihistamines,

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Table 2 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine bladder	Ketamine bladder treatment
							corticosteroids; in severe cases, substitution cystoplasty considered; abstinence to prevent progression
Jhang et al., 2017	Retrospective comparative study	Chronic ketamine abuse; mean 4.5 y; ketamine cystitis	53 (M 25/F 28)	Mean 28 y (18–43)	Mean 4.5 y	Ulcerative cystitis; reduced bladder capacity (<100–300 ml); thickened bladder wall; hydronephrosis, vesicoureteral reflux; severe bladder pain; urgency; frequency; hematuria	Symptomatic therapy (NSAIDs, intravesical hyaluronic acid/ onabotulinumtoxinA); partial cystectomy + AE (augmentation enterocystoplasty) with/ without ureteral reimplantation; intermittent self-catheterization
Lamers et al., 2022	Case report	Intranasal; 7 g/week escalating to 20–30 g/week over 6 months	1 (M 1/F 0)	18 y	≈6 months	Ulcerative cystitis with bladder capacity as low as 18 cc (urgency, frequency, nocturia, suprapubic pain, incontinence, gross haematuria); bilateral vesicoureteral reflux; hydroureteronephrosis	Anticholinergics and β3-agonist; IV antibiotics; bilateral ureteral stents; Foley catheter
Lee et al., 2009	Narrative review (78 reported cases + local illustrative case report)	Chronic street ketamine (powder smoked/snorted, oral ingestion); months–years	78 (M 48/F 30); local illustrative: single young male	Mean 25 y	Months-years	Severe ulcerative/ haemorrhagic cystitis; contracted bladder; hydronephrosis; ureteric strictures; renal impairment; papillary necrosis	Symptomatic: anticholinergics, intravesical pentosan sulfate, corticosteroids; obstruction relief: double-J stenting, nephrostomy; refractory: bladder augmentation or cystectomy with neobladder
Lee et al., 2015	Case series	Snorting 1–10 g/ day; duration 2–15 y	9 (M 4/F 5)	Mean 31 y (25–42)	2–15 y (mean ~ 8 y)	All showed severe LUTS; ulcerative ureteritis; bilateral unephrosis; ureteral strictures & polyps; 7 cases of AKI	Bilateral ureteroscopy with double-J stents; long-term stents; antibiotic therapy for acute pyelonephritis
Li et al., 2019	Cross-sectional survey	106 rehabilitation clients; 92.9% daily use; snort 34%, smoke 33%, both 33%; <10 g/day; mainly used several times per day; mean 75 mo use	106 (M 95/ F 11)	Mean 24.9 y (SD 6.4)	Mean 75 mo (~6 y)	LUTS onset ~25 mo; frequency, urgency, nocturia, dysuria, hematuria, bladder pain; symptom scores correlate with duration; snorting associated with more severe LUTS than smoking	Oral meds; bladder hydrodistention; hyaluronic acid instillation; intravescical botox; hyperbaric O_2
Liao et al., 2018	Case report	Intranasal inhalation; initially once weekly, escalating to once every 2–3 days, up to ~10 g/day	1 (M 1/F 0)	29 y	3 y	Severe LUTS (dysuria, frequency, urgency); bilateral hydronephrosis; hydroureters; thickened bladder wall; bladder diverticulum; at cystoscopy: trabeculation, follicular neoplasms	TURP; resection of bladder follicular lesions
Lin, Lin et al., 2016	Case report	Inhalation 0.2–3 g/ day for 12 y	1 (M 1/F 0)	28 y	12 y	LUTS (frequency, urgency, hematuria)	NR
Liu et al., 2021	Cross-sectional case-control, urinary proteomics + targeted metabolite analysis	Chronic recreational self-administration of ketamine (mean 4.0 ± 2.2 g/day; last use ≈ 6 ± 6 days before sampling)	56 KA (41 M, 15 F)‖40 HC (25 M, 15 F)	≈ 31.3 ± 6.3 y (KA)	All ketamine abusers met DSM-IV-TR criteria for ketamine dependence; chronic self-administration (mean 4.0 ± 2.2 g per day during the 90 days before admission; last use ≈ 6 ± 6 days before sampling; 85% consumed >2 g/day)	Yes – 51% OABSS >6; urinary RBC > 5 HPF = 23%, WBC > 5 HPF = 39%	None (observational)

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Table 2 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine bladder	Ketamine bladder treatment
Manongi et al., 2022	Case report	Recreational ketamine ≥10 y; dose/route NR	1 (M 0/F 1)	29 y	10 y	Severe bilateral hydronephrosis; bladder & ureteral wall thickening	Bilateral nephrostomies; later ureteral stents
Marongiu et al., 2025	Case series	Recreational intranasal/ combined use; doses NR; acute ED presentations	3 (M 1/F 2)	22–36 y	NR	Acute urinary retention (1/ 3)	Catheterization
Meng et al., 2015	Pilot case series	Intravesical hyaluronic acid for ketamine cystitis; failed oral meds; mean abuse 68 mo	5 (M 1/F 4)	Mean 22 y (SD 1.5)	Mean 5.7 y (68 mo)	Severe ketamine-associated cystitis >6 months; FBC 14–255 ml	Intravesical hyaluronic acid instillations
Misra et al., 2014	Retrospective cohort	Inhalational ketamine 1/week–5 g/day; duration 1–10 y	34 (M 27/F 7)	Median 23 y (17–45)	1–10 y	Small inflamed bladder 60–350 ml; haematuria/ pyuria; ulcers; 6% hydronephrosis	Medical therapy (analgesics, antimuscarinics, antibiotics, cimetidine, steroid); hydrodistention; ulcer diathermy; cystectomy
Ng et al., 2013	Retrospective case series	Chronic ketamine abuse 3–15 y; all resumed use post-surgery	4 (M 1/F 3)	21–30 y (mean 27)	3–15 y	Irritative urinary symptoms, contracted bladder (mean 37 ml), hydronephrosis, VUR	Anti-inflammatory agents, antimuscarinic agents and analgesics, with no significant clinical improvement; ileal augmentation cystoplasty; later PCN & ureteric repair
Okunlola et al., 2024	Case report	Chronic intranasal use; 3 g sniffed 3 days before admission; >1 year of abuse	1 (M 1, F 0)	24 years	> 1 year of chronic ketamine misuse	Ketamine bladder with hematuria, hydroureteronephrosis	Bilateral nephrostomy; flexible cystoscopy/ planned cystectomy; abstinence
Peng et al., 2016	Case report	≈5 g/day for 1 y; stopped >1 y before augmentation enterocystoplasty; route NR	1 (M 0/F 1)	28 y	1 y	Contracted bladder 39 ml; severe frequency, hematuria	Intravesical hyaluronic acid; augmentation enterocystoplasty
Rahman et al., 2024	Case report	5 g/day for 2 years, stopped 7 years ago	1 (M 0, F 1)	34 y	Heavy daily ketamine use for 2 years	Ketamine cystitis with dysuria, hematuria; ureteral obstruction, hydronephrosis	Repeated bilateral ureteral stents; antibiotics; periodic monitoring
Schifano et al., 2021	Pharmacovigilance database analysis	Medicinal ketamine (IV, nasal, oral); 1–7500 mg; 1 day–>1 y exposure	1758 (F 1157/M 561/Not specified)	Adults 18–64 y (most)	Variable; many 1 mo–1 y	1758 renal/urinary ADRs: AKI, oliguria, hematuria, cystitis, hydronephrosis	NR
Selby et al., 2008	Case report	Regular intranasal snorting for 2 years; last use days before admission	1 (M 1/F 0)	26 y	2 y	Bilateral hydronephrosis; inflammatory cystitis; obstructive nephropathy	Bilateral nephrostomies; dialysis; common bile duct stent
Shahzad et al., 2012	Case report	Oral analgesic ketamine 60 mg QDS (240 mg/day) for chronic pain; 3 y use	1 (M 1/F 0)	52 y	3 y	Severe ketamine cystitis with dysuria, hematuria and nocturia; bladder capacity 29 ml; bilateral ureteric reflux	Intravesical cystistat; pentosan; oxybutynin; nerve sparing cystoprostatectomy and ileal conduit formation
Smart, Cattermole et al., 2013	Case report	Chronic intranasal ketamine; 1–2 g/day for 2–3 y then 2 g 2–3×/week; 10 y total; abstinent 4–5 month	1 (M 1/F 0)	30 y	10 y	Small-capacity bladder; severe frequency, dysuria, nocturia and testicular pain (ketamine cystitis)	Apha-blocker (tamsulosin) followed by an anticholinergic (oxybutynin), both for 3 months; Intravesical chondroitin sulphate 0.2% weekly×6 then monthly;
Sturgess et al., 2023	Retrospective cohort	Recreational ketamine users with KIU; dose NR; 2011–2022 cohort	81 (M 59/F 22)	Median 30 y (IQR 27–34)	NR	Storage lower urinary trac symptoms, pelvic pain; small bladder capacity; hydronephrosis 24.7%; ureteric strictures; subtotal cystectomy in 1	Anticholinergic/β-3 agents; cystodistension; intravesical cystistat/ Botox; nephrostomy; cystectomy
Tam et al., 2014	Cross-sectional study in prospective cohort	Mean 18.5 g/week; duration 81 mo; active 214 vs ex-abusers 104	318 (M 144/ F 174)	Mean 24.4 ± 3.1 y (Crock et al., 2012; Gonzalez-Cadavid	6.8 y	Severe LUTS; mean (SD) PUF score 21.2(7.8); mean (SD) voided volume 111.5 (110)mL; Mean(SD) bladder capacity 153 ml	Diclofenac sodium or COX-2 inhibitors Additional anticholinergic and opioid analgesics

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Table 2 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine bladder	Ketamine bladder treatment
				et al., 2000; Guo et al., 2002; Hu et al., 2009; Jiang et al., 2014; Juneja et al., 2024; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Page et al., 2021; Reijerkerk et al., 2010; Roncero et al., 2025; Svendsen et al., 1999; Tang et al., 2014; Verma et al., 2025; Zhuo, 2002)		(126); bladder emptying efficiency 73.3 (26.9) %. 5% of patient had +urine culture; 8.1% had unilateral or bilateral hydronephrosis.	
Tan et al., 2021	Retrospective cohort study	NR	53 (M 40/F 13)	Mean 25 y (13–38)	Mean 3 y	Ketamine cystitis, Contracted bladder (MCC < 100 ml), severe LUTS.	Bladder autoaugmentation by transurethral vesicomyotomy (BATV) increased capacity to 281 ml; bladder hydrodistention (BH) to 214 ml
Tran et al., 2014	Case report	Ketamine 3–5×/day for 4 y; heavy abuse;	1 (M 1/F 0)	24 y	4 y	Contracted irregular bladder symptoms included fever, chills, urinary frequency, dysuria, urgency, and more recently, urinary incontinence	Antibiotics; outpatient urology follow-up
Wong et al., 2013	Case report	Ketamine insufflation	1 (M 1/F 0)	26 y	>4 y chronic use	Bladder dysfunction	Foley catheter drainage
Yang et al., 2020	Case series	0.1–3 g 2–19×/ week;	18 (M 18/F 0)	Mean 24.5 y (Chang et al., 2012; Chu et al., 2008; Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Jiang et al., 2014; Juneja et al., 2024; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Reijerkerk et al., 2010; Roncero et al., 2025; Shahani et al., 2007; Svendsen et al., 1999; Tang et al., 2014; Tsai et al., 2009; Zhuo, 2002)	2.1–4 y	Bladder contracture, reduce bladder volume (<120 ml), hydronephrosis; urinary leukocyte, urinary erythrocyte, urinary albumin.	Cystectasia; Foley catheter; irrigation
Yee et al., 2015	Prospective case series	Mean 15.7 g/week; 70%	319 (205/ 258)	Mean 25 y ± 3.8	Mean 6.9 y	LUTS; Pain means Functional bladder	First line: FANS (diclofenac-etoricoxib),

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Table 2 (*continued*)

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine bladder	Ketamine bladder treatment
		≥7 uses x/week; 15% 1–3 uses x/ week; 10% 4–6 uses x/week; 4.6% uses <1 uses per week.				capacity (FBC) 142 ml; some hydronephrosis	anticholinergic (solifenacin) and phenazopyridine and paracetamol. Second line opioid (tramadol) and pregabalin. Third line intravesical sodium hyaluronate. Fourth line surgery
Zeng et al., 2017	Prospective case series	NR	36 (M 30/F 6)	Mean 26 y (19–38)	1–5 y	Ketamine associated cystitis. Increased frequency and urgency of urination, and urinary incontinence, nocturia. Abnormal bladder shape, low bladder capacity, and bladder wall thickening. Cystoscopy showed mild hyperemia or erythematous patches in the bladder.	The patients had been treated before the study whit: muscarinic receptor blocker and/or antibiotics. Then during this study: Cystoscopy intra bladder injection of botulinum toxin A 200 IU, then hydrodistention with saline. Cefuroxime for those with positive culture
Zhong et al., 2015	Case report	Intranasal ketamine abuse; 5 y; dose	1 (M 1/F 0)	31 y	5 y	Bladder leiomyosarcoma; macroscopic hematuria	Partial cystectomy

M = male; F = female; SD = standard deviation; LUTS = lower urinary tract symptoms; VUR = vesicoureteral reflux; AKI = acute kidney injury; FBC = functional bladder capacity; OABSS = Overactive Bladder Symptom Score; RBC = red blood cells; WBC = white blood cells; HPF = high-power field; NSAIDs = non-steroidal anti-inflammatory drugs; AE = augmentation enterocystoplasty; DJ stent = double-J ureteral stent; TURP = transurethral resection of the prostate; PCN = percutaneous nephrostomy; IV = intravenous; IM = intramuscular; NR = not reported; ADR = adverse drug reaction; MCC = maximum cystometric capacity; BH = bladder hydrodistention; BATV = bladder autoaugmentation by transurethral vesicomyotomy; COX-2 = cyclooxygenase-2; ICU = intensive care unit.

Interventions based on traditional Chinese medicine are reported as described in the original studies; however, their outcomes may involve both physiological and psychological effects and should, therefore, be interpreted cautiously.

Early recognition and abstinence were consistently emphasized. Multiple studies underscored the importance of maintaining a high index of suspicion for ketamine use in young patients presenting with unexplained LUTS, psychiatric symptoms, and/or atypical medical complications. Prompt identification of ketamine misuse may allow for early cessation, which was strongly associated here with symptom improvement and prevention of irreversible bladder and renal damage.

Multidisciplinary care emerged as a key principle. Urologists, psychiatrists, nephrologists, and addiction specialists should be jointly involved in patient management activities. In emergency settings, clinicians should consider gastrointestinal, urological, and neuropsychiatric sequelae of ketamine and ensure referral to substance use treatment services for sustained abstinence. Occupational and professional risks were also highlighted, especially for healthcare providers with access to ketamine.

A range of different pharmacological interventions were reported in selected contexts:

- Naltrexone and lamotrigine showed potential benefit in reducing craving and supporting abstinence.
- Antidepressants (duloxetine, SSRIs) and antipsychotics (haloperidol, paliperidone) were useful for the treatment of comorbid mood disorders, ketamine-induced psychosis, and withdrawal symptoms.
- Adjunctive treatments such as chondroitin sulfate or hyaluronic acid instillations improved bladder function.
- Non-pharmacological approaches included motivational interviewing, cognitive-behavioural therapy, family-oriented interventions, Virtual Reality-based cognitive rehabilitation, and culturally tailored models such as the Kawa occupational therapy
- Framework (Hsiao et al., 2024). Integrated harm-reduction programmes, particularly in chemsex populations, were reported to improve engagement with mental health services and reduce relapse rates.

Summarizing current collated evidence, the management of urological complications may require a stepwise approach:

- Initial conservative treatment (analgesia, anticholinergics, intravesical instillations).
- Escalation to invasive urological procedures (hydro-distention, augmentation entero-cystoplasty, cystectomy) considered in refractory cases, with abstinence as a pre-requisite for surgical success.
- Close monitoring of renal function, recognition of unusual infections (e.g., *Pantoea septica pneumonia*), and attention to multiorgan toxicity (hepatobiliary, pulmonary, neurological).

Overall, clinical recommendations converged here on three pillars: early diagnosis, absolute cessation of ketamine, and multidisciplinary, individualized, care supported by both medical and psychosocial interventions.

Given the heterogeneity of presentation, improved clinician education is needed to facilitate earlier recognition of ketamine misuse and its associated complications, especially when patients present with non-specific or atypical psychiatric, urological, gastrointestinal, or neurological symptoms.

4. Discussion

To the best of our understanding, the present systematic review provides the most comprehensive synthesis to date of clinical interventions for ketamine misuse and its related complications. The findings highlight both the complexity of the clinical presentations and the heterogeneity of treatment approaches, underscoring the urgent need for evidence-based protocols.

Table 3
Clinical studies and case reports describing "K-cramps" (abdominal and pelvic pain) in chronic ketamine users, with details on patterns of use, symptomatology, and therapeutic approaches.

Name, year	Study design	Administration	Population (N, M, F)	Mean age ± standard deviation	Abuse/ dependence	Ketamine cramps	Ketamine cramps treatment
Avra et al., 2024	Case report	Inhalational 0.5–1 g/ day for 3 y plus IM/IV 1–3 g/day for 8 mo (chronic heavy use)	1 (M 1/F 0)	31 y	≈ 3 y + 8 mo	Severe, recurrent upper abdominal pain, worse postprandially, recurrent with ketamine re-use deep aching/cramping sensation, was worse after eating and improved with fasting	Supportive measures (hot baths, small meals, hot beverages) 4 milligram IV morphine and 1 liter lactated Ringer's IV fluid. Ibuprofen and acetaminophen
Chang, Huang et al., 2016	Case report	Snorting 6 g/day for 8 y; increased to 10 g/ day; dependence	1 (M 1/F 0)	38 y	8 y heavy use	Recurrent abdominal cramping associated with chronic ketamine abuse; multiple emergency visits	Abstinence; symptoms resolved after cessation of use
Chang et al., 2012	Case series	Mean daily 3.2 g; abuse 2–36 mo; LUTS onset at 12.7 mo	20 (M 13/F 7)	Mean 25.8 y (Crock et al., 2012; Gonzalez-Cadavid et al., 2000; Guo et al., 2002; Hu et al., 2009; Kolhekar & Gebhart, 1994; Lin, Lin et al., 2016; Svendsen et al., 1999; Zhuo, 2002)	Mean 12.7 mo	Severe gastric cramping reported by about 30% of frequent k users	NR
Chung et al., 2014	Surgical case series	Chronic abuse mean 3.82 y; contracted bladder 50 ml	14 (M 4/F 10)	Mean 26.7 y	Mean 3.82 y	Severe pelvic-abdominal pain	AE with or without ureteral reimplantation
Critchlow, 2006	Case report	Daily snorting 1–7 g/ day for 6 y	1 (M 1/F 0)	25 y	6 y	Non-specific abdominal pain with loss of appetite and weight loss	Ketamine abstinence
Huang et al., 2008	Case report	IV ketamine 2–3×/ week for ~6 mo; symptoms within several days of starting use	1 (M 1/F 0)	25 y	~6 mo	Suprapubic pain reported	NR
Huang et al., 2016	Case report	Smoking then snorting 4–5 g/day (6–10 uses/ day) for 3 y; ongoing cravings	1 (M 1/F 0)	25 y	3 y	Abdominal pain reported	NR
Manongi et al., 2022	Case report	Recreational ketamine ≥10 y; dose/route NR	1 (M 0/F 1)	29 y	10 y	Sharp, epigastric pain for two weeks	NR
Marongiu et al., 2025	Case series	Recreational intranasal/combined use; doses NR; acute ED presentations	3 (M 1/F 2)	22–36 y	NR	Severe lower abdominal pain and bladder cramps, bladder cramps during a follow-up visit one year later (1/3)	2.5 mg oxybutynin
Misra et al., 2014	Retrospective cohort	Inhalational ketamine 1/week–5 g/day; duration 1–10 y	34 (M 27/F 7)	Median 23 y (17–45)	1–10 y	Abdominal pain reported	Analgesics and other treatments referred to urinary symptoms
Ng et al., 2013	Retrospective case series	Chronic ketamine abuse 3–15 y; all resumed use post-surgery	4 (M 1/F 3)	21–30 y (mean 27)	3–15 y	One patient had severe pelvic pain	Anti-inflammatory agents, antimuscarinic agents and analgesics, with no significant clinical improvement
Peng et al., 2016	Case report	≈5 g/day for 1 y; stopped >1 y before augmentation enterocystoplasty; route NR	1 (M 0/F 1)	28 y	1 y	Lower abdominal pain (pain score, 8 out of 10) >1 y	No
Rahman et al., 2024	Case report	5 g/day for 2 years, stopped 7 years ago	1 (M 0/ F 1)	34 y	Heavy daily ketamine use for 2 years	Bilateral flank pain, severe back pain	NR
Schifano et al., 2021	Pharmacovigilance database analysis	Medicinal ketamine (IV, nasal, oral); 1–7500 mg; 1 day–>1 y exposure	1758 (F 1157/M 561/Not specified)	Adults 18–64 y (most)	Variable; many 1 mo–1 y	Lower abdominal/ suprapubic pain was reported as part of ketamine-induced uropathy (KIU)	Ketamine abstinence, anti-inflammatory and anticholinergic drugs, + opioids if pain persisted
Selby et al., 2008	Case report	Regular intranasal snorting for 2 years; last use days before admission	1 (M 1/F 0)	26 y	2 y	Colicky abdominal pain, increasing flank pain	NR

M = male; F = female; SD = standard deviation; NR = not reported; IM = intramuscular; IV = intravenous; ED = emergency department; LUTS = lower urinary tract symptoms; AE = augmentation enterocystoplasty; KIU = ketamine-induced uropathy.

4.1. Ketamine addiction

The evidence on ketamine dependence is largely derived from case reports and small case series, with only a limited number of controlled studies available. Patients presenting with ketamine-related complications are predominantly young adults (typically aged 20–35 years), often male, and frequently characterized by psychiatric comorbidities and polysubstance use, which can complicate both diagnosis and management. However, the variability observed across studies suggests that ketamine misuse may affect a broader population, underscoring the importance of maintaining a high index of clinical suspicion across different age groups. Management strategies were highly variable, ranging from symptomatic care to pharmacological interventions (benzodiazepines, SSRIs, naltrexone, lamotrigine, gabapentinoids) and psychotherapeutic approaches (motivational interviewing, cognitive-behavioural therapy, occupational therapy). While abstinence remains the primary determinant of clinical outcomes, achieving and maintaining abstinence often depends on the adequate treatment of underlying psychiatric comorbidities, such as mood and anxiety disorders. Targeting these symptoms may reduce self-medication patterns and craving, thereby improving engagement with treatment and reducing relapse risk. The prevalence of ketamine-induced psychosis remains difficult to determine, as the available evidence is largely based on case reports and heterogeneous observational studies rather than systematic epidemiological investigations.

Recent evidence has begun to explore pharmacological strategies for ketamine use disorder, including the potential role of agents targeting craving and relapse prevention (e.g., naltrexone, lamotrigine, and other neuromodulatory approaches). However, current data remain limited and largely derived from small studies or case reports, highlighting the need for further controlled clinical trials (Verma et al., 2025). The relationship between psychiatric comorbidity, addiction mechanisms, and treatment response remains complex and not yet fully understood. Ketamine misuse frequently occurs in individuals with mood and anxiety disorders, suggesting that self-medication processes and shared neurobiological pathways may contribute to the development and maintenance of dependence (Chiappini et al., 2025; Marongiu et al., 2025; Schifano et al., 2021). From a mechanistic perspective, growing evidence suggests a potential involvement of the opioid system in ketamine's reinforcing effects, which may help explain the observed benefits of opioid antagonists such as naltrexone in reducing craving and relapse (Verma et al., 2025). However, these hypotheses remain preliminary and require further investigation through controlled studies.

Furthermore, the increasing medical use of ketamine and esketamine in psychiatric and pain management settings also raises important considerations regarding the potential risk of misuse, diversion, and long-term safety (Chiappini et al., 2025). This evolving clinical landscape underscores the need for careful patient selection, monitoring, and follow-up in order to minimize unintended non-medical use.

Multidisciplinary interventions appeared to be the most effective, particularly when addiction specialists and mental health services were integrated with medical care. However, relapse was common, and long-term follow-up data were scarce. This underscores the need for robust clinical trials to assess the efficacy and safety of pharmacological and psychosocial interventions specifically targeting ketamine use disorder.

4.2. Ketamine-induced bladder dysfunction (KBD)

Ketamine-induced bladder dysfunction (KBD) emerged as one of the most serious and well-documented medical consequences. A recent systematic review had already addressed the potential complications associated with therapeutic use of both ketamine and esketamine (Chiappini et al., 2025). LUTS and reduced bladder capacity were reported in nearly all chronic users, with severe cases progressing to hydronephrosis, ureteral strictures, and renal impairment. Treatment approaches suggested were stepwise, ranging from conservative pharmacotherapy and intravesical instillations to invasive urological procedures, including augmentation entero-cystoplasty and cystectomy (see Fig. 2), which should be interpreted as a pragmatic, narrative-based clinical framework rather than a formal guideline. Abstinence from ketamine was the single most important determinant of outcome, but structural damage was often irreversible, particularly in long-term users. These findings emphasize the importance of early recognition; screening for ketamine misuse in young patients with unexplained LUTS; and close urology referral.

4.3. K-cramps

“K-cramps” represent an under-recognized but disabling complication. Although their pathophysiology remains unclear, the condition appears closely linked to ketamine-induced urinary dysfunction, suggesting a possible shared mechanism involving chronic inflammation and smooth muscle dysfunction. Reported management strategies are mainly symptomatic and include analgesics (e.g., NSAIDs and opioids), antispasmodic agents, anti-inflammatory drugs, and supportive care, although these approaches often provide only partial relief. In contrast, symptom resolution is most consistently observed following ketamine cessation, which appears to be the most important determinant of clinical improvement. Future research should aim to better characterize the pathophysiology of “K-cramps”, differentiate gastrointestinal from urological contributions, and evaluate targeted treatment strategies through prospective and controlled studies.

4.4. Pathophysiological perspective

Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, and these receptors are widely expressed in urogenital organs, including the penis, prostate, and human bladder (Gonzalez-Cadavid et al., 2000). From a pathophysiological perspective, several mechanisms have been proposed to explain the visceral and urological manifestations associated with ketamine misuse. NMDA receptor activation can excite neurons in the spinal dorsal horn and facilitate nociceptive transmission in the spinal cord, playing a central role in the development of visceral hyperalgesia (Guo et al., 2002; Kolhekar & Gebhart, 1994; Zhuo, 2002), and potentially contributing to the severe abdominal pain described in “K-cramps”. In parallel, NMDA receptors appear to be involved in mediating inflammatory pathways (Svendsen et al., 1999), and animal studies suggest that they modulate both inflammatory and non-inflammatory bladder nociception (Crock et al., 2012; Hu et al., 2009).

Furthermore, some studies suggest that ketamine may induce microvascular changes in the bladder, leading to endothelial injury and impairment of intrinsic microcirculation (Lin, Lin et al., 2016), ultimately contributing to fibrotic remodeling during chronic ketamine exposure (Jiang et al., 2014; Lin, Lin et al., 2016; Reijerkerk et al., 2010). Progressive fibrosis of the urinary bladder following chronic inflammation may reduce bladder capacity, resulting in severe urinary frequency with very short voiding intervals (Tang et al., 2014). Consistently, histological findings in patients with ketamine-induced cystitis have demonstrated chronic inflammation, mucosal ulceration, and infiltration of neutrophils and lymphocytes (Chang et al., 2012; Chu et al., 2008; Shahani et al., 2007; Tsai et al., 2009). Overall, these mechanisms are likely to be interrelated and remain largely hypothetical, reflecting the current limitations of the available evidence.

Table 4
Clinical considerations and recommendations derived from the included studies on ketamine misuse and related complications, including implications for diagnosis, management, and follow-up.

Name, Year	Recommendation for clinicians
Avra et al., 2024	ED clinicians should consider GI and urological sequelae of chronic ketamine and link patients to SUD care for maintain abstinence
Bhad et al., 2016	Naltrexone may aid ketamine dependence; professionals at risk
Boccio et al., 2025	Recognize "K-cramps" in ED; inquire about chronic ketamine use
Caloro et al., 2018	NMDA poly-abuse can mimic schizophrenia; screen for novel psychoactives in psychosis
Chao & Shai, 2010	Duloxetine improved LUTS and mood in ketamine user
Yiu-Cheung, 2012	Abstinence is essential; monitor LUTS
Chang, Rajagopalan et al., 2016	Heavy chronic ketamine use linked to major depression; abstinence leads to rapid remission
Chang et al., 2012	Ketamine-induced uropathy affects upper & lower tracts; cessation critical; hydrodistention helps
Chen & Wang, 2012b	Early cessation rapidly reverses LUTS; maintain high suspicion of ketamine use in young patients with unexplained LUTS
Chen et al., 2020	Depression severity predicts craving; treating depression may improve withdrawal outcomes
Chen et al., 2022	CoNS skin infection after IV ketamine; antibiotics & debridement
Chen et al., 2013	Ketamine vasospasm can cause renal infarction; early imaging and cessation essential
Cheung et al., 2014	Urinary EGF may serve as biomarker and help guide therapy for ketamine cystitis
Chung et al., 2014	Enterocystoplasty restores capacity; relapse undermines success – abstinence essential
Critchlow, 2006	Ketamine withdrawal syndrome treatable with benzodiazepine and vitamin detoxification
Giannini et al., 2000	Haloperidol significantly reduced BPRS scores in acute ketamine intoxication; useful option in ED care
Goyal et al., 2014	Occupational exposure risk; need complete abstinence & monitoring
Hamza & Bryson, 2011	Avoidance of triggering agents, surgical teams should set relapse-prevention plans for recovering ketamine-using, full disclosure of substance use history to all care providers
Hoskins, 2009	ED staff should recognize ketamine cystitis as an emerging clinical entity; prompt urology referral; cessation of ketamine use strongly associated with symptom improvement
Hsiao et al., 2024	Kawa model therapy is culturally responsive and non-stigmatizing, may boost motivation and engagement for abstinence; clinicians may consider integrating it in early-phase SUD interventions
Huang et al., 2008	Ketamine cystitis can progress to ESRD; early recognition and cessation of ketamine are essential.
Huang et al., 2016	Lamotrigine may reduce ketamine craving and facilitate cessation; consider lamotrigine in patients with dual diagnosis (e.g., mood disorder + KUD); clinicians should monitor for adverse effects and titrate lamotrigine slowly
Hung et al., 2019	IMB programme improves motivational stage and halves one-year relapse rate relative to standard education (1-year relapse: 50% IMB vs 75% EAU)
Hung et al., 2023	Prioritize integrated harm-reduction strategies covering sexual health, mental health, and substance use; intention to reduce chemsex predicts mental-health service uptake; need comprehensive integrated services
Jalil & Gupta, 2012	Take detailed social drug histories in young patients with persistent LUTS; be aware of ketamine's potential to cause irreversible bladder damage; refer early to urology; support abstinence
Jhang et al., 2017	Patients with MBC <100 ml or <300 ml with upper tract damage benefit from early AE; conservative management if bladder damage is not advanced; encourage complete cessation
Kyaw et al., 2024	Rare pleuropulmonary *Pantoea septica* (or even uncommon gram-negative pathogens) infection possibly related to ketamine-induced immunosuppression; need high suspicion, prompt microbiological diagnosis and fast targeted antibiotics
Lamers et al., 2022	KIU can progress rapidly; consider ketamine use in young patients with refractory LUTS; early diagnosis and cessation of ketamine critical to prevent irreversible bladder and renal damage
Lee et al., 2005	Screen for substance abuse (including ketamine) in young diabetics; adopt a harm-reduction approach, tailor insulin regimens for high-risk periods (e.g., weekends, parties); integrate addiction support into diabetes care to improve adherence/reduce morbidity
Lee et al., 2009	In young patients with severe LUTS and sterile urine, consider ketamine abuse; early diagnosis and cessation crucial to prevent irreversible bladder/renal damage; multidisciplinary management with addiction support and early urology referral essential
Lee et al., 2015	Upper-tract ketamine damage, evaluate it in patients with LUTS; stenting relieves obstruction and preserve renal function; monitor kidneys; cessation of ketamine essential
Lee, Chopra et al., 2024	Combined GABA-glutamate modulation reduced ketamine cravings and use; warrants further study to confirm efficacy
Li et al., 2019	LUTS severity tracks consumption duration; snorting worse than smoking; intravesical therapy more effective; cessation of ketamine key
Liao et al., 2019	Ketamine-linked inflammation may cause early BPH; surgery relief of obstruction; abstinence key to prevent recurrence and preserve renal function
Lim, 2003	Considering high abuse potential of ketamine; dose-related psychotic symptoms; in polysubstance abuse and acute multimodal hallucinations or psychosis, ketamine intoxication should be considered
Lin, Lin et al., 2016	Withdrawal-related depression/anxiety may resolve without medications; monitor
Liu, Zerbo et al., 2015	Ketamine showed transient antidepressant effect and potential role in treating craving in patients with alcohol addiction; long-term risks warrant caution
Liu et al., 2021	Urinary APOA1 proposed as non-invasive biomarker; monitor OABSS/pain to detect and manage ketamine-induced cystitis
Lu et al., 2016	Ketamine abuse can induce persistent mania; monitor mood changes
Man, 2020	VR-based cognitive rehabilitation enhances cognition and employability in abstinent ketamine users
Manongi et al., 2022	Severe KIU with cholangiopathy; early nephrostomy protects kidneys
Marongiu et al., 2025	Rising ketamine incidents; include ketamine in routine toxicological screens; early urological follow-up
Maxwell & Spence, 2005	Distinct profiles by drug; impairment high; integrate mental-health & drug treatment
Meng et al., 2015	HA gives short-term pain & voiding relief; larger long-term studies needed
Misra et al., 2014	Abstinence most effective; early multidisciplinary approach & substance-misuse liaison essential
Ng et al., 2013	Simple surgical management of the contracted bladder may produce only sub-optimal outcomes; abstinence from drug use should be stressed; the option of a simple ileal conduit should also be discussed prior to surgical intervention
Okunlola et al., 2024	Multidisciplinary management; early recognition of multi-organ toxicity; ketamine abstinence is crucial
Peng et al., 2016	AE effective for refractory ketamine cystitis; pregnancy feasible after surgery; abstinence essential
Rahman et al., 2024	Suspect ketamine abuse in young patients with uropathy; importance of early diagnosis, abstinence, and regular follow-up
Roxas et al., 2021	Possible ketamine withdrawal syndrome; monitor and taper gradually
Schifano et al., 2021	Medicinal ketamine can still cause KIU; monitor renal/urinary function; restrict chronic high-dose use
Selby et al., 2008	Ketamine metabolite precipitation can obstruct the renal tract; suspect ketamine in unexplained hydronephrosis & multi-organ dysfunction
Shahzad et al., 2012	Therapeutic ketamine can cause severe KIU requiring cystectomy; early cessation advised
Sharma et al., 2024	Chronic ketamine can induce SOD; early ERCP and cessation prevent hepatobiliary damage

(*continued on next page*)

Table 4 (*continued*)

Name, Year	Recommendation for clinicians
Smart, Kabir et al., 2013	Chondroitin sulphate may restore bladder function;
Sturgess et al., 2023	A stepwise approach, primarily focusing on ketamine cessation, counselling, and chronic pain services. Initial medical therapy anticholinergic/β-3 agonist titrated to response. Invasive treatments after 6 months of abstinence
Tam et al., 2014	Female sex and higher weekly dose worsen symptoms; abstinence is protective
Tan et al., 2021	BATV offers greater bladder capacity than BH with similar safety; minimally invasive
Tang et al., 2013	Heart/Kidney Yin-Yang deficiency patterns predominate; individualized TCM assessment needed
Tran et al., 2014	POCUS useful for KAUD diagnosis; cessation is mainstay
Tsai et al., 2020	Treated with intravenous normal saline (4000 ml/day) together with alkalization procedures. Then received a series of 13 hemodialysis sessions
Tung et al., 2014	Chinese SDS-K shows high reliability (α 0.74) and validity; scores correlate with use patterns
Unterrainer et al., 2014	Neurofeedback plus psychotherapy effective in adolescent ketamine misuse
Weiner et al., 2000	Ketamine intoxication short-lived; Treatment consists primarily of supportive care, benzodiazepines for sedation, and the prevention of rhabdomyolysis with i.v. fluids in agitated patients
Wang et al., 2016	Family-oriented therapy reduces relapse and improves social/academic status
Wang, Chen, Lin, Chong et al., 2018	Ketamine abstinence is more likely to be persistent compared with abstinence from stimulants
Wong et al., 2013	Intra-alveolar pressure following the Valsalva's manoeuvre during insufflation of ketamine can cause Pneumomediastinum. Pneumomediastinum from ketamine sniffing resolves conservatively
Yang et al., 2020	Cystectasis is a safe and effective procedure that improves LUTS and ketamine associated urinary dysfunction (KAUD)
Yee et al., 2015	Tiered protocol improves symptoms; abstinence and lower weekly dose predict better outcomes
Zeng et al., 2017	Combo therapy markedly improves LUTS; Intra bladder injection of botulinum toxin A is useful in refractory KAC
Zhong et al., 2015	Chronic ketamine abuse may contribute to rare bladder leiomyosarcoma; consider early screening
Zuccoli et al., 2014	Paliperidone effective for ketamine psychosis; minimal CYP metabolism useful

SUD = substance use disorder; LUTS = lower urinary tract symptoms; KIU = ketamine-induced uropathy; KUD = ketamine use disorder; ESRD = end-stage renal disease; CoNS = coagulase-negative *Staphylococcus*; EGF = epidermal growth factor; MBC = maximum bladder capacity; AE = augmentation enterocystoplasty; BPH = benign prostatic hyperplasia; APOA1 = apolipoprotein A1; OABSS = Overactive Bladder Symptom Score; VR = virtual reality; IMB = Information-Motivation-Behavior program; EAU = education-as-usual; HA = hyaluronic acid; SCD = subacute combined degeneration; ERCP = endoscopic retrograde cholangiopancreatography; SOD = Sphincter of Oddi dysfunction; BATV = bladder autoaugmentation by transurethral vesicomyotomy; BH = bladder hydrodistention; TCM = traditional Chinese medicine; POCUS = point-of-care ultrasound; SDSK = Severity of Dependence Scale for Ketamine; ADR = adverse drug reaction; CYP = cytochrome P450.

4.5. Recommendations for clinicians

The review of clinical recommendations highlighted converging priorities: early recognition, complete cessation of ketamine use, and multidisciplinary management. Several pharmacological options (e.g., naltrexone, lamotrigine, paliperidone) showed promise in isolated cases, but these approaches may well require validation in controlled studies. Psychosocial interventions, including motivational enhancement, family-oriented therapy, VR-based rehabilitation, and culturally adapted frameworks such as the Kawa model, were reported to enhance abstinence and engagement, particularly in high-risk populations such as those involved in chemsex. Integrated harm-reduction strategies that address sexual health, mental health, and substance use simultaneously appeared as especially valuable.

4.6. Final considerations

Taken together, the findings underscore ketamine misuse as a significant and multifaceted clinical problem, with profound psychiatric, urological, and systemic consequences. Abstinence remains the cornerstone of treatment, but supportive care, pharmacological strategies, and structured psychotherapeutic interventions can play a critical role in mitigating symptoms and improving outcomes. Future research should prioritize well-designed controlled studies, standardized treatment protocols, and multidisciplinary models of care that integrate psychiatric, medical, and addiction services. Such efforts are essential to provide clinicians with evidence-based tools to address the growing challenge of ketamine misuse.

5. Limitations

The strength of the current evidence is limited by the predominance of case reports and small observational studies, with only a very limited number of controlled or randomized trials available, which significantly restricts the ability to establish causal relationships between interventions and outcomes. Substantial heterogeneity exists across the included studies in terms of patient characteristics (e.g., age, psychiatric comorbidities), patterns of ketamine use (e.g., dosage, route of administration, duration), and types of interventions applied, preventing direct comparisons and limiting the possibility of robust meta-analytic conclusions. The frequent presence of polysubstance use, along with co-occurring psychiatric and medical conditions, further complicates the attribution of observed effects specifically to ketamine. In addition, some included studies were not primarily focused on ketamine misuse but were incorporated due to partial relevance (e.g., studies examining ketamine pharmacology in healthy volunteers or specific subpopulations, as well as cohorts in which ketamine was not the predominant substance), introducing additional heterogeneity and potential bias. This overall variability in study design, populations, and outcomes precluded any quantitative synthesis, supporting instead the use of a narrative approach. Furthermore, the generally low methodological quality of the included studies and the lack of long-term follow-up data, particularly regarding relapse prevention and the durability of urological or psychiatric interventions, limit the generalizability and strength of the findings. Therefore, the results of this review should be interpreted with caution and considered primarily hypothesis-generating rather than definitive.

6. Conclusions

This systematic review demonstrates that ketamine misuse is associated with a broad spectrum of psychiatric, urological, and systemic complications, often requiring complex and multidisciplinary management. The available evidence indicates that abstinence is the most effective measure to halt progression of both psychiatric and somatic harm, although irreversible bladder and renal damage may occur in long-term users.

Overall, current management strategies remain fragmented and largely based on case-level evidence. There is an urgent need for high-quality prospective studies and the development of standardized treatment algorithms. Clinicians should maintain a high index of suspicion for ketamine misuse in young patients with unexplained urological or psychiatric symptoms, to ensure early referral to appropriate services, and adopt integrated, individualized, and multidisciplinary approaches.

CRediT authorship contribution statement

Alessio Mosca: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Stefania Chiappini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Andrea**

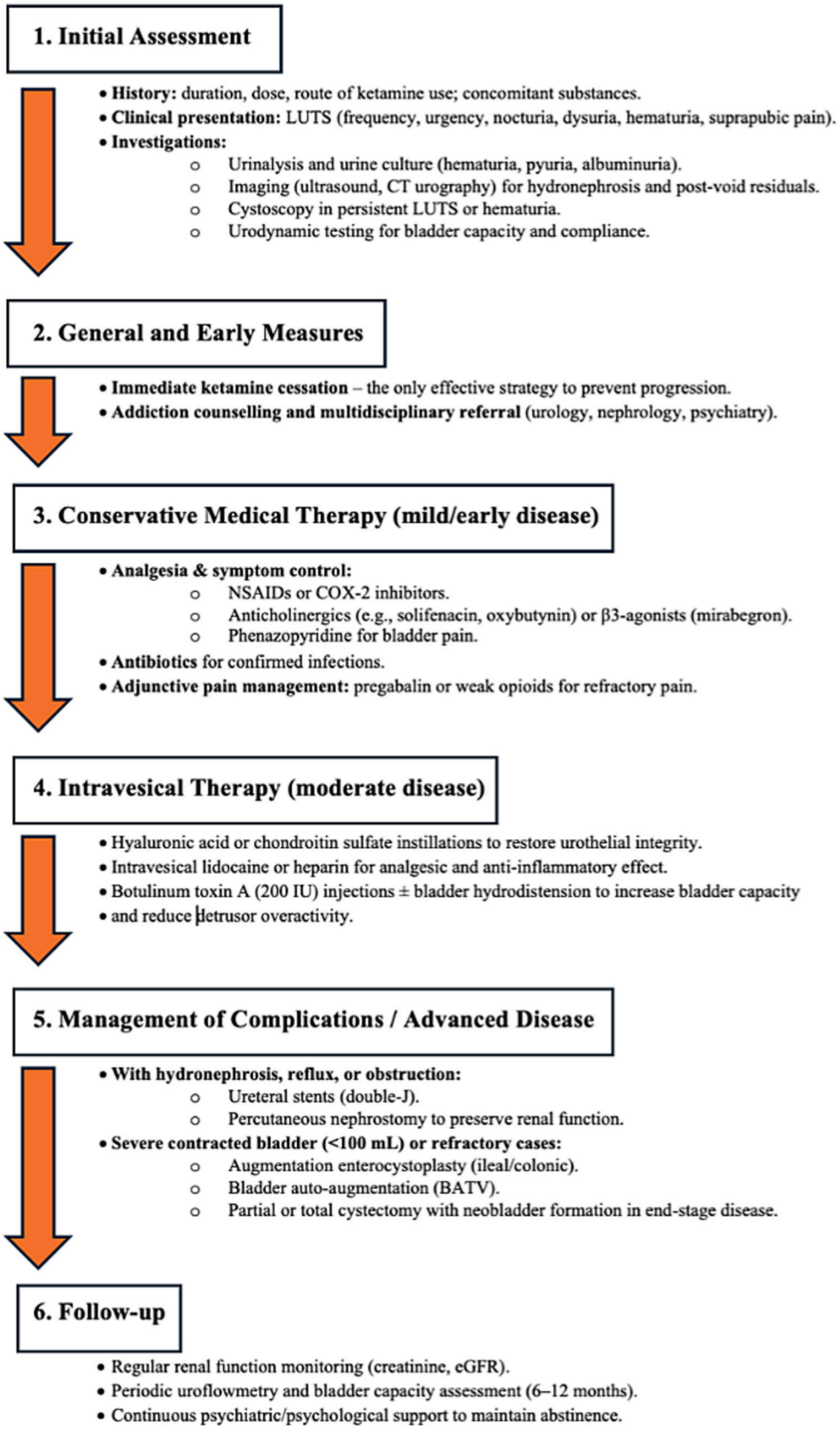

Fig. 2. Proposed treatment algorithm for ketamine-induced bladder dysfunction (KBD).

Miuli: Software, Methodology, Investigation, Formal analysis, Data curation. **John Martin Corkery:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Formal analysis. **Tommaso Piro:** Investigation, Formal analysis, Data curation. **Rita Allegretti:** Investigation, Formal analysis, Data curation. **Nicola Ciraselli:** Investigation, Formal analysis, Data curation. **Carlotta Marrangone:** Investigation, Formal analysis, Data curation. **Nicolo' Schifano:** Writing – review & editing, Visualization, Validation, Investigation, Conceptualization. **Mauro Pettorruso:** Visualization, Validation, Supervision. **Giovanni Martinotti:** Visualization, Validation, Supervision. **Fabrizio Schifano:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization.

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Declaration of competing interest

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Data availability

Not applicable.

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