Ketamine use in young people

Dr James O'Toole

Honorary Senior Lecturer

Bangor University

Non-prescribed ketamine use is rising in the UK
(Guerrini et al 2025 British Medical Journal)

- The rise in non-prescribed use of ketamine across the UK in recent years is concerning because of potential effects on physical and mental wellbeing
- Despite its classification as a class B drug under the Misuse of Drugs Act 1971, public awareness of the risks and long term harms associated with ketamine remains insufficient
- Ketamine is used clinically as a general anaesthetic, with subanaesthetic doses prescribed for pain and treatment resistant depression
- Recent studies have shown promise for its use in the treatment of post-traumatic stress disorder
- Intranasal esketamine is licensed for treatment of depression (but not approved by the National Institute for Health and Care Excellence)

Non-prescribed ketamine use is rising in the UK
(Guerrini et al 2025 British Medical Journal)

- Ketamine is increasingly used recreationally at individual doses of 250 mg or more producing euphoria and dissociative states
- Its low cost has made it popular among young people, particularly 16-24 year olds
- The prevalence of self-reported use in the past year in this age group rose from 1.7% to 3.8% between 2010 and 2023
- More individuals are seeking treatment for addiction - number of people starting treatment for ketamine addiction in 2023-24 was 3609 (eight times higher than in 2014-15)
- Ketamine use disorders remain inadequately defined within current classification systems

Mechanism of action of ketamine:

- **N-methyl-d-aspartate (NMDA) Receptors:**
- ketamine blocks NMDA receptors which contributes to potent anaesthetic and analgesic properties
- ketamine is a racemic mixture containing equal parts of (R)- and (S)-ketamine (with (S)-enantiomer possessing stronger affinity for the NMDA receptor)
- **Opioid Receptors:**
- ketamine can bind to and activate mu (μ) and delta (δ) opioid receptors
- analgesic and antidepressant effects can be blocked by naltrexone
- **Monoaminergic Receptors:**
- ketamine inhibits uptake of noradrenaline, dopamine and serotonin

Mechanism of action of ketamine:

- **Muscarinic Receptors:**

- ketamine profoundly inhibits muscarinic signalling (contributing to central and peripheral anticholinergic effects)

- **Voltage-Sensitive Ca Ion Channels:**

- ketamine interacts with voltage-sensitive Ca ion channels, resulting in ketamine mediated or modulated analgesic effects

- **Hyperpolarization-activated cyclic nucleotide channels (HCN1) Receptors:**

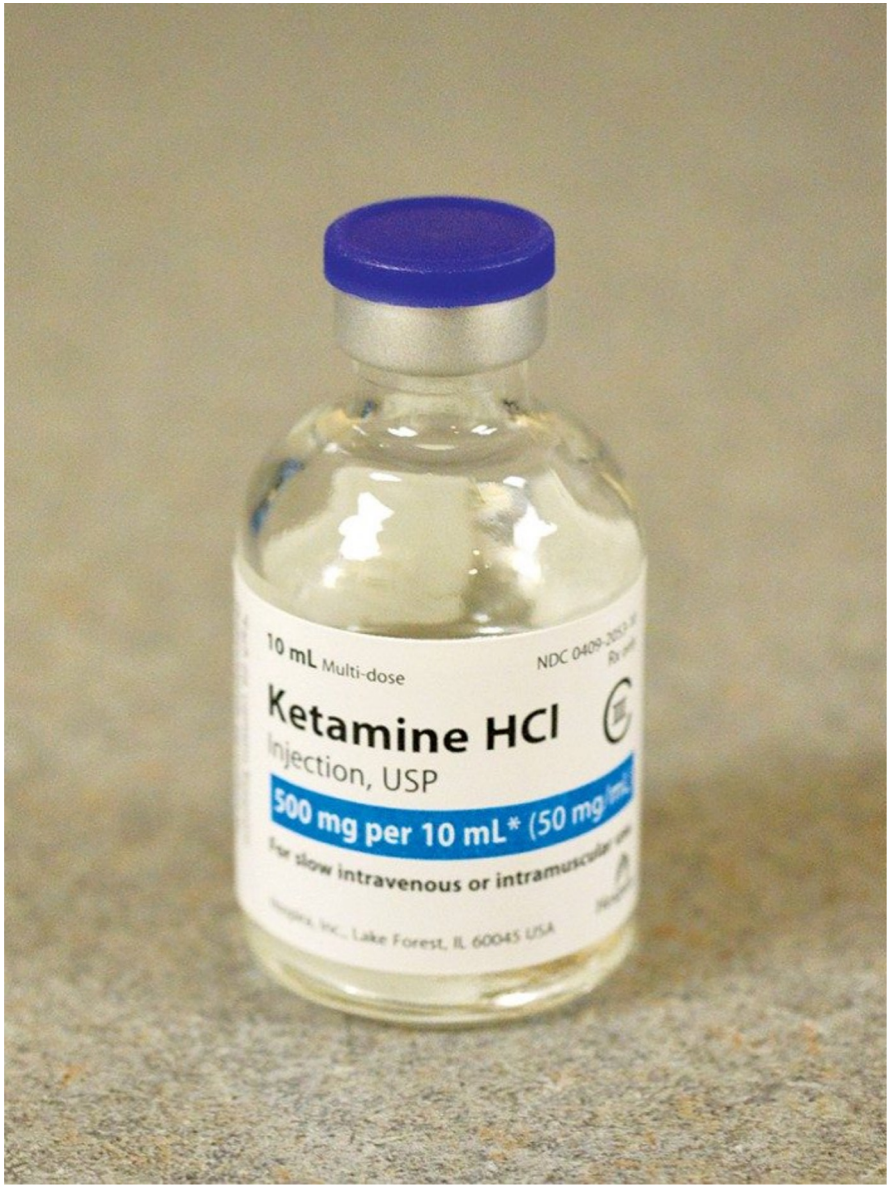
- hypnotic effects of ketamine appear to be primarily mediated by inhibition of NMDA and HCN1 receptors

What does ketamine look like?

- Ketamine is white/transparent when pure sold as a fine powder or tiny crystals (although the powder can be other colours, such as off-white or brown)

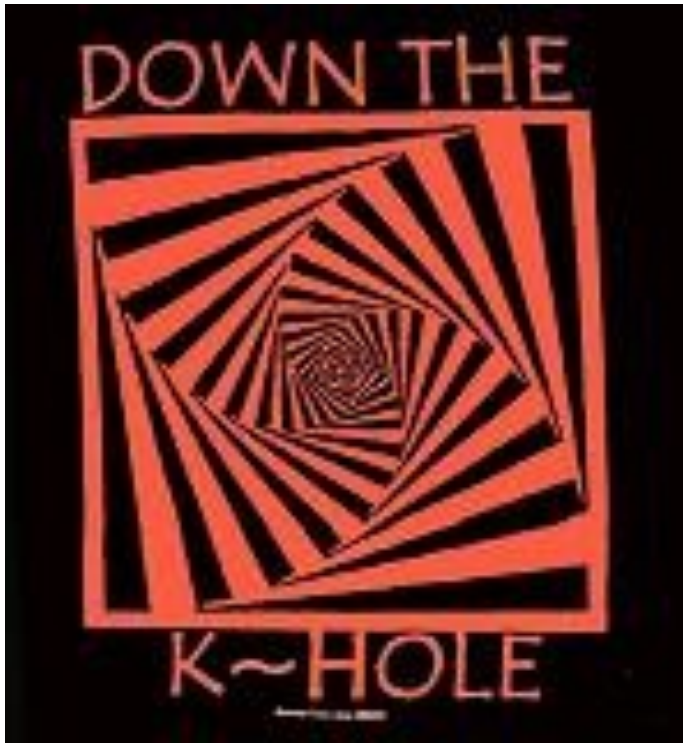
- Ketamine also comes in pills (although this is less common) - ketamine pills may be sold to unsuspecting users as another drug e.g. ecstasy

- Ketamine is a clear liquid, when used in medicine or veterinary practice- some people obtain ketamine in liquid form (or dissolve it) and inject it for a faster and more intense effect


10 mL Multi-dose
Ketamine HCl
Injection, USP
500 mg per 10 mL* (50 mg/mL)
Lake Forest, IL 60045 USA

Esketamine nasal spray:

Effects of ketamine



Effects of ketamine:

- Medical ketamine use is a safe, controlled treatment used in specific conditions while recreational use is illegal, unregulated and potentially unsafe

- Dosing and side-effect profile associated with medical ketamine prescribing (e.g. 2mg/kg for 5-10 minutes of sedation as a one-off) contrasts with sustained recreational use where individuals can regularly use 3.5g/day or more over long periods of time

Effects of ketamine

- Dose related effects on recreational ketamine users have been observed:

- at low doses, stimulant effects predominate and the effect of environmental conditions are significant

- at higher doses, psychedelic effects predominate and the effect of the environment diminishes

Drug interactions

- People who die or end up in hospital after taking ketamine have often combined ketamine with other drugs, particularly alcohol
- Commonly, polydrug use involves alcohol, cannabis or cocaine (and more)
- Taking ketamine with stimulants (such as cocaine and ecstasy) may cause tachycardia and hypertension
- Taking it with depressant drugs (such as alcohol, benzodiazepines or heroin) may cause unconsciousness, respiratory depression or aspiration

Risks of ketamine use

- At large doses, ketamine can cause acute psychological effects including severe dissociation (the ‘k-hole’)
- ketamine toxicity presentations can include impaired consciousness, agitation, hallucinations, delirium, confusion, dissociative effects, nausea, tachycardia and mild hypertension
- such presentations are generally short-lived (4-12 hours) and usually do not need pharmacological interventions
- K-cramps: regular users can get severe abdominal pain often called k-cramps (cause is unknown but they seem distinct from the bladder pain)

Deaths following illicit ketamine use in England, Wales and Northern Ireland 1999-2024: An update report to inform the reclassification debate (Pullen et al 2025 J Psychopharmacol)

Results: There were 696 deaths identified with illicit ketamine between 1999 and 2024. Annual deaths increased over 10-fold from 2014 (15 deaths) to 2024 (197 deaths)

Whilst absolute deaths implicating illicit ketamine rose (2014: 6 deaths; 2023: 123 projected deaths), the proportion of deaths where illicit ketamine was implicated in causing death declined (2014: 60.0% of cases; 2024: 42.6% of cases)

Concurrently, polydrug use increased (median number of co-administered substances 1999-2004: 3; 2005-2009: 3, 2010-2014: 4, 2015-2019: 6; 2020-2024: 6), and the demographic profile of decedents shifted towards greater deprivation and dependence-related context

Discussion: There has been an acceleration in deaths following illicit ketamine in recent years, which are increasingly featuring complex patterns of polydrug use and socio-economic vulnerability.

Policy responses must extend beyond single-substance legislative controls to encompass harm reduction, treatment integration, and social support strategies

Comorbid health conditions

- People with psychotic disorder, or who have ever suffered a psychotic episode, should avoid ketamine as it may precipitate psychosis and – psychotic symptoms may persist beyond the period when the drug is active

- Drugs which radically affect consciousness are more likely to cause panic and fear in people who suffer from anxiety normally

- Ketamine increases heart-rate and blood pressure - effects are usually mild but could be dangerous for people with related health problems or who combine it with other drugs

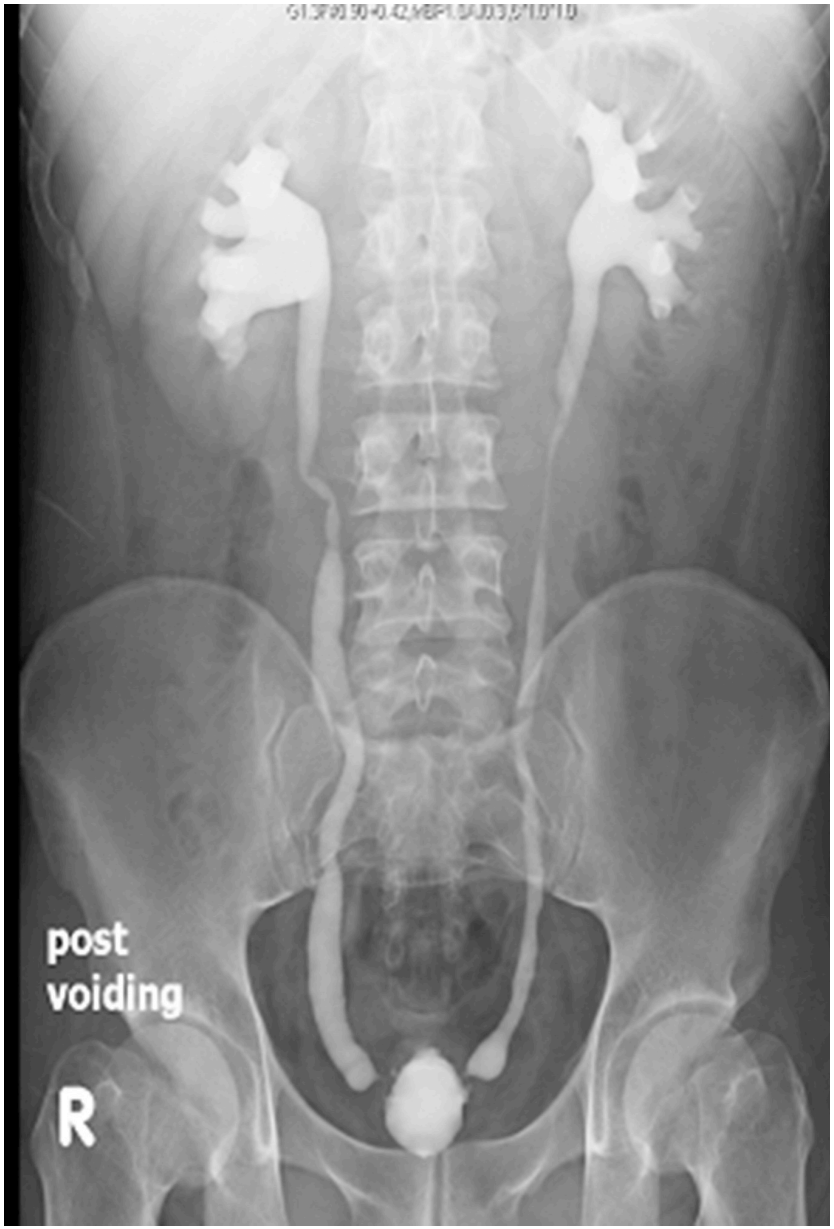
Ketamine harm

- Acute harms of ketamine use relate to vulnerability and injuries
- Long term use can seriously harm both physical and mental health, quality of life, personal relationships, and impair academic or professional performance
- Cognitive impairment and psychiatric comorbidities are often observed in people who use ketamine long term
- Severe depressive symptoms have been reported in 35% of long term users (and an association with trauma, deliberate self harm and suicidal ideation)

Physical harm

Physical harms related to ketamine use include:

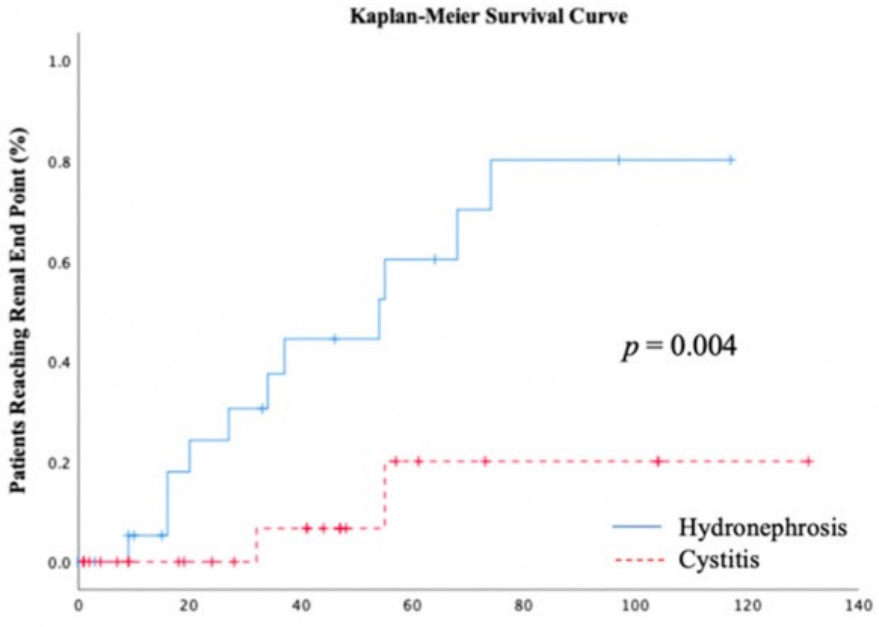
- **urinary tract:** ulcerative cystitis with LUTS and ultimately a contracted fibrotic bladder but also upper tract involvement with hydronephrosis, hydroureter and obstructive uropathy
- **hepatobiliary effects:** cholestatic liver injury (bile duct dilatation, microscopic bile duct injury and hepatic fibrosis)
- abnormal LFT (raised alkaline phosphatase and raised transaminases) suggest hydronephrosis and vice versa
- **weight loss:** loss of appetite, nausea and vomiting can cause significant and sustained weight loss (cachexia)



Intravenous urogram:

IVU in a man with ketamine uropathy showing bilateral hydronephrosis and hydroureter with contracted urinary bladder

Patients reaching endpoint - 30% reduction in eGFR or End Stage Renal Disease is significantly greater in hydronephrosis group v cystitis group:



Number at risk							
Hydronephrosis	22	12	8	5	2	1	0
Cystitis	29	17	14	5	3	3	1

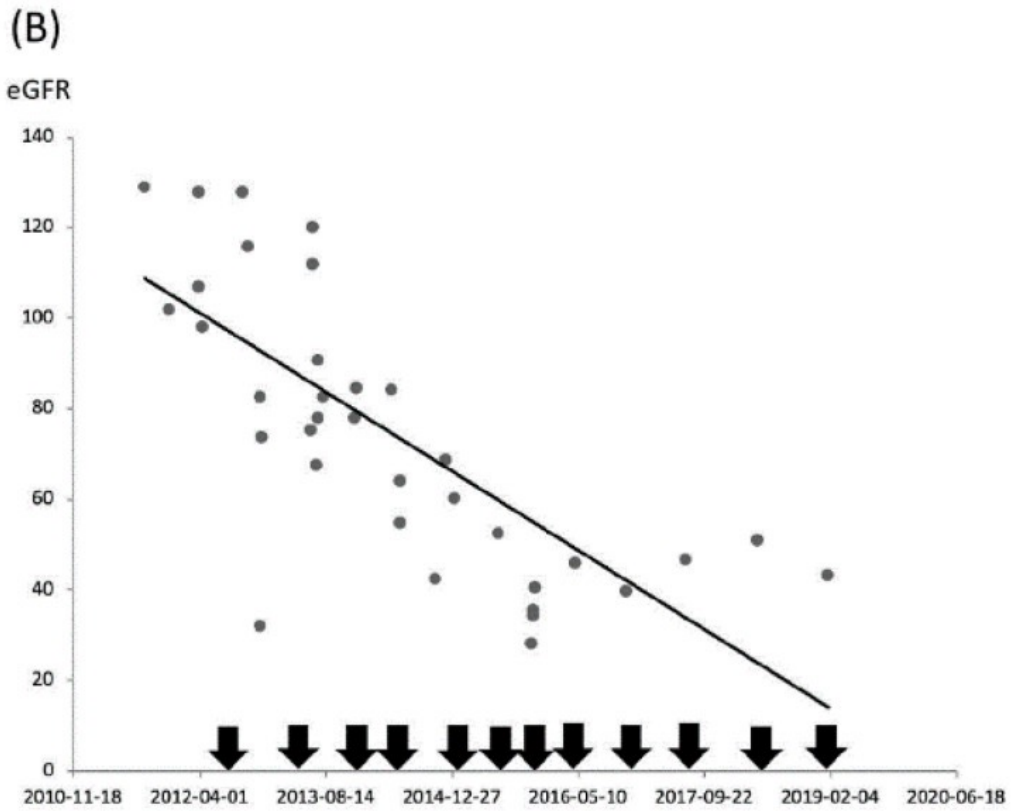
Shih-Isiang Ou et al 2020

Patient B

Patient B is a 27-year-old woman who underwent regular double-J stent exchanges every 6 months

Decline in eGFR occurred despite regular follow up and management with stenting

Shih-Isiang Ou et al 2020



Treatment for ketamine dependence

- Patients report that healthcare professionals may be unaware that ketamine can cause addiction
- Addiction services are primarily based on psychosocial approaches that are not substance specific
- People who use ketamine report that services lack an understanding of ketamine addiction with no specific interventions (patients are usually offered detox and rehab)
- No specific medication to date but case studies suggest that benzodiazepines mitigate ketamine withdrawal and naltrexone supports relapse prevention (no clinical trials or formal observational research on either intervention - evidence of low quality e.g. case reports)

Ketamine addiction

- ICD-11 criteria for dependence include:

- subjective sensation of urge or craving to use ketamine
- physiological features of dependence such as tolerance to the effects of the drug and withdrawal symptoms following cessation of use
- impaired ability to control use in terms of onset and duration of use
- increasing priority given to drug use over other activities including family, work and leisure activities, and
- persistence of use despite harm or negative consequences

Ketamine tolerance

- Ketamine tolerance - individuals require higher doses of ketamine to achieve the desired effects, such as dissociation or euphoria
- tolerance can develop rapidly with frequent use - users may not experience severe physical withdrawal symptoms but can have strong cravings
- more often ketamine is used and the higher the doses, the faster tolerance develops
- regular users find that the initial doses no longer produce the same effects, prompting them to increase their intake

Ketamine withdrawal:

- Ketamine withdrawal is mainly psychological with some physical symptoms:

- ketamine craving is common
- feeling anxious, irritable and low in mood
- brain fog, hard to concentrate, memory problems
- insomnia and weird dreams

But in some cases:

- fatigue, headaches, nausea, sweating, tremor, palpitations
- intense agitation, panic attacks, low mood and feelings of hopelessness
- worsening bladder symptoms may also lead to relapse

Ketamine withdrawal time line:

- Day 1: ketamine cravings, anxiety, low mood, agitation, fatigue and insomnia
- Day 2-4: ketamine cravings peak, with worsening psychological symptoms (low mood and poor concentration) and worsening bladder symptoms
- Day 5-7: over the peak with cravings coming in waves and still feeling tired but better sleep and able to think more clearly
- Week 2: moving on from acute ketamine withdrawal although some may experience craving and anxiety over several weeks

Symptomatic Management of Ketamine-induced Cystitis

- Cessation or abstinence of ketamine use is the first line of treatment and is most effective in managing KIC (but difficult for frequent users despite understanding the benefit of cessation)
- studies on KIC abstinence have demonstrated improved KIC symptoms compared to disease progression in patients who fail to discontinue ketamine use
- large survey study by Winstock et al (2012), found that among 1285 recent ketamine users, more than a quarter (340) reported LUTS (27%)
- higher doses or more frequent use of ketamine were associated with significantly higher rates of symptom
- 51% symptomatic users reported improvement in urinary symptoms upon cessation of use

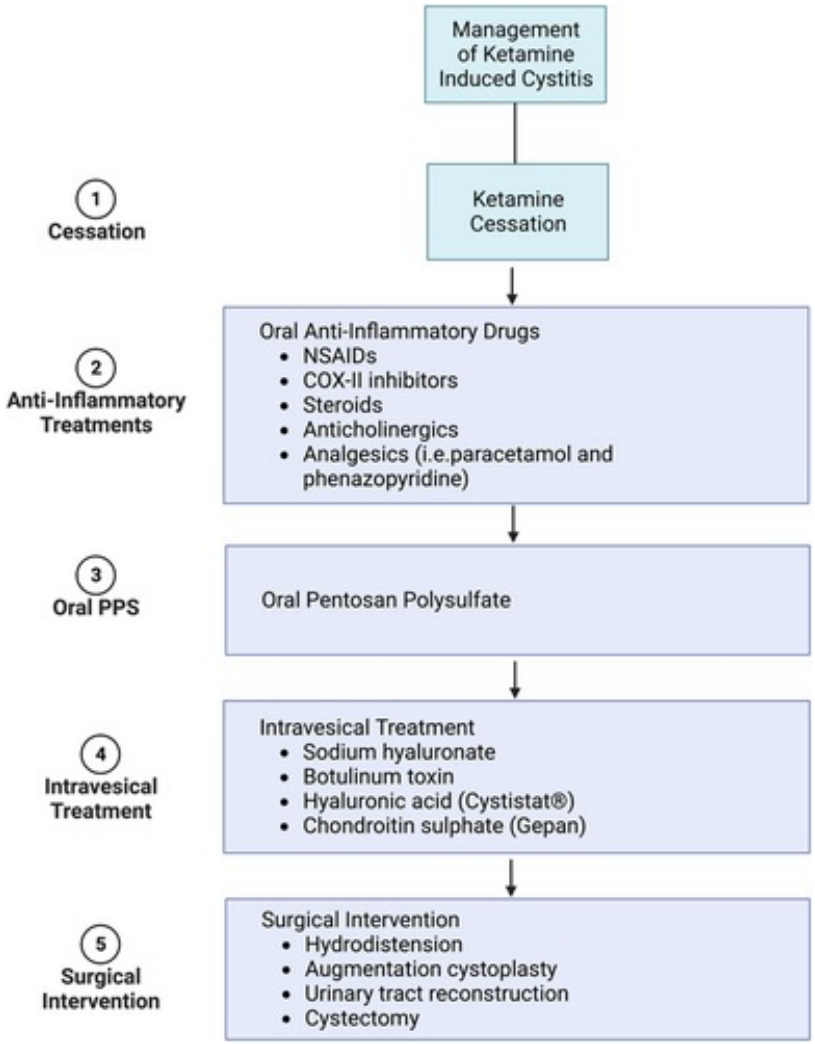
Staging system for ketamine uropathy

- Wu et al (2017) proposed classification of ketamine uropathy in 3 stages:

- Stage 1 (inflammatory phase) where cessation of ketamine use and oral medication can help to reverse bladder changes

- Stage 2 (structural changes to bladder occur) treatment includes bladder instillations and botulinum A injections to detrusor muscle

- Stage 3 (end stage bladder fibrosis with upper urinary tract involvement) requiring surgical intervention



Zhou et al 2023

Symptomatic Management of Ketamine-induced Cystitis

- No agreed pharmacological management for bladder pain in KIC

First line:

- simple analgesics e.g. NSAIDs ?selective Cox-2 inhibitors (e.g. celecoxib or meloxicam)
- anticholinergics (e.g. solfenacin or oxybutynin) or beta-3 agonists (mirabegron) for overactive bladder

Second line:

An analgesic ladder of NSAIDs, opioid analgesics and drugs for neuropathic pain such as amitriptyline, gabapentin and pregabalin has been successfully used for bladder pain (Hong et al 2018)

Symptomatic Management of Ketamine-induced Cystitis

- Zhou et al (2023) describe the use of opioids and pregabalin for pain in KIC with symptomatic improvement in 67.7% patients
- abstinence from ketamine and amount of ketamine used affect treatment response
- strategy developed in Bristol involving buprenorphine patches with co-codamol and amitriptyline at night gave adequate symptom control to allow cessation of ketamine use (Wood et al 2011)

Harm reduction:

- Infrequent use of ketamine (3 days per week or less) is linked to less physical and mental health comorbidity
- harm reduction requires early engagement of users with health advice and early intervention when problems arise

- Limited interventions available for young people using ketamine
- do not relate to mutual support groups aimed at older class A drug users
- limited availability of inpatient detoxification and residential rehabilitation (especially for anyone under 18 years of age)