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Rising incidence of recreational ketamine use: Clinical cases and management in emergency settings

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ABSTRACT

The recreational use of ketamine has risen significantly in the Netherlands, particularly among young adults in nightlife settings. This trend has been accompanied by an increase in first aid incidents involving ketamine, often in combination with other substances such as alcohol or MDMA, leading to heightened toxicity. Acute intoxication with ketamine manifests through symptoms like agitation, hallucinations, nausea, tachycardia, and hypertension, while frequent use is associated with long-term complications, including ketamine-induced uropathy. Although ketamine is not currently included in standard toxicological screenings, its detection can aid in diagnosing mixed intoxications, excluding alternative causes, and facilitating referral to follow-up care. Routine inclusion of ketamine in toxicological screening could improve diagnostic precision and better address the health risks associated with its growing prevalence.

1. Introduction

1.1. Ketamine's growing prevalence in Europe

The European Union Drugs Agency (EUDA) reports that ketamine is increasingly available and prominent in Europe's drug-related challenges [1]. Ketamine seized in Europe is predominantly imported from countries like India, Pakistan, and China, transiting through nations including the Netherlands and Belgium [1]. In the Netherlands, there is evidence of illicit ketamine production, with at least four production sites dismantled between 2017 and 2021 [1]. The increasing availability of ketamine through both diversion from legitimate sources and illicit manufacturing has contributed to its rising recreational use. Recreational users frequently administer ketamine intranasally in its powder or crystal form; however, intravenous or intramuscular injection in liquid form, as well as oral consumption of the powder or crystal form, is also reported.

1.2. Ketamine use trends in the Netherlands

In the Netherlands, ketamine's popularity as a recreational drug has shown significant growth, leading to a growing concern regarding its use and addiction. According to the Health Survey/Lifestyle Monitor by CBS, the National Institute for Public Health and the Environment, and the Trimbos Institute, ketamine use among adults increased from 0.6 % in 2018 to 1.2 % in 2023 [2]. Among young adults in nightlife settings, usage is notably higher [3]. In a 2023 internet survey of 16–35-year-olds who had visited a nightclub or festival within the past year, a quarter (25 %) reported ketamine use in the last year [3]. Alarmingly, one-fifth of these users reported monthly use, and 3 % reported weekly use [3]. This trend is particularly pronounced in urban areas with vibrant nightlife scenes, such as Amsterdam and Rotterdam [4]. When compared to other European countries, the Netherlands exhibits higher rates of ketamine use among young adults, reflecting its liberal drug policies and active nightlife culture [4].

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1.3. Health risks and emergency department challenges

Ketamine-related health incidents have increased significantly in the Netherlands, posing challenges for Emergency Departments (ED) and general practitioners [5]. According to the Trimbos Institute's Drug Incident Monitor (MDI), 6 % of the 6411 drug-related incidents reported in 2022 involved ketamine, often in combination with alcohol or other substances [5].

At OLVG, a major city hospital in Amsterdam, the ED handles approximately 70,000 patient visits annually, with care provided by emergency physicians. In 2023, 19 cases of ketamine intoxication were identified at OLVG based on patient history, with observation frequently being the only required intervention. Urine toxicological screening is performed when clinically indicated, utilizing a competitive fluorescence immunoassay (Triage TOX Drug Screen, Alere, San Diego, Inc. 9975, USA). However, ketamine is not part of the standard panel and must be specifically requested by the attending emergency physician.

Research indicates that ketamine use is associated with a significantly higher incidence of lower urinary tract symptoms (LUTS) compared to the general population [6]. Specifically, the risk of LUTS is six times greater among ketamine users than among non-drug users [6]. Healthcare professionals in the Netherlands are increasingly concerned about the rising prevalence of ketamine addiction and ketamine-induced uropathy, particularly in frequent users.

1.4. Pharmacological and toxicological characteristics of ketamine

Ketamine ((R,S)-ketamine) is a racemic mixture of (S)(+)- and (R)(-)-enantiomers, used clinically since the 1970s as a fast-acting anesthetic, with the S-enantiomer (Ketanest-S, Esketiv) used in medical practice, while the racemic mixture is mainly consumed recreationally [7]. In the clinical field, ketamine is utilized for chronic pain management and psychiatric disorders [8, 9, 10]. However, there are no standardized guidelines for its medical use. The lack of consensus on dosing and administration protocols complicates efforts to distinguish between therapeutic and non-medical use, potentially influencing public perception and complicating policy development [11].

Pharmacokinetically, ketamine's high lipophilicity and large volume of distribution (3–5 L/kg) enable rapid penetration into the central nervous system [7]. Its low oral and intranasal bioavailability (16–55 %) results from extensive first-pass metabolism, primarily via cytochrome P450 (CYP) 3A4, producing the active metabolite norketamine with reduced pharmacological potency [12]. Following parenteral administration, ketamine and norketamine exhibit elimination half-lives of approximately 2.5–4 h, supporting its rapid onset and central effects [12].

The toxicological profile of ketamine is dose-dependent, with effects influenced by co-ingested substances [12]. Recreational doses (e.g., 60–250 mg intranasally, 200–300 mg orally, 50–100 mg intravenously), cause hallucinations, motor impairment, altered pain perception, cognitive disruptions, euphoria, and dissociation [12,13]. Higher doses may induce a "K-hole," characterized by profound dissociation and immobility, resembling near-death experiences [12]. Symptoms of intoxication include impaired speech, hypertension, tachycardia, nausea, abdominal pain, anxiety, agitation, and urinary retention [12, 13]. Fatal outcomes are rare but occur with high mono-doses (e.g., 1000 mg IV) or mixed intoxications [14,15]. Co-administration of ketamine with central nervous system depressants, including alcohol and benzodiazepines, enhances sedation and increases the risk of respiratory depression [13]. Conversely, stimulants such as MDMA and cocaine exacerbate ketamine's sympathomimetic effects, manifesting as tachycardia, hypertension, and hyperthermia [7, 12, 15]. Furthermore, the presence of adulterants like levamisole intensifies the compound's toxicological risks [5].

1.5. Societal impacts of ketamine misuse

Beyond immediate health risks, ketamine use can adversely affect various aspects of life, including academic performance, employment, and interpersonal relationships [4,16]. In the Netherlands, there is growing recognition of these broader societal impacts, prompting calls for comprehensive public health campaigns to raise awareness and provide support for individuals affected by ketamine misuse.

1.6. Study objective and clinical relevance

The rise in ketamine-related incidents, coupled with its dual use in medical and recreational contexts, has prompted healthcare providers to call for enhanced preventive measures and policy interventions to address this growing problem [17]. In this study, we describe three cases treated in a Dutch hospital ED following ketamine use, often in combination with other substances. We discuss the clinical toxicology, drug testing, and management of ketamine intoxication, emphasizing the relevance of addressing urological complications and incorporating ketamine in routine toxicological screenings.

2. Cases

2.1. Patient A

A 36-year-old woman vomited at a party and became unresponsive. Upon ambulance arrival, she did not respond to pain stimuli. She had consumed four units of alcohol and inhaled ketamine via a vaporizer two hours earlier. Upon arrival at the ED, she was responsive but experienced double vision and instability. The routine urine toxicological screening, which does not test for ketamine, was negative for all recreational drugs included in the panel, including amphetamines, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cocaine, phencyclidine, methadone, opiates, prescription benzodiazepines, and tetrahydrocannabinol (THC). Comprehensive toxicological screening was not conducted. Since ketamine is not included in standard toxicological testing and confirmatory testing was not conducted, its presence could not be retrospectively confirmed in this case. Physical examination showed no abnormalities, and after a few hours she was discharged home after observation.

2.2. Patient B

A 22-year-old woman with a history of depression and suicidality was found unconscious by her father, with labored breathing. She had admitted to taking several oxazepam tablets of unknown strength combined with ketamine and alcohol. Although, she denied suicidal intent, she acknowledged recent heavy ketamine use and admitted addiction. In the ED, she experienced frequent apneas, vomiting, agitation, and slightly dilated pupils. Similar to Patient A, no comprehensive toxicological screening for ketamine was performed. The toxicological screening detected oxazepam and was negative for other recreational drugs in the panel, including amphetamines, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cocaine, phencyclidine, methadone, opiates, and tetrahydrocannabinol (THC). As ketamine was not included in the routine toxicology panel and confirmatory testing was not performed, its presence could not be retrospectively validated in this case. After four hours, she was stable and discharged home with a psychiatric referral. She is on a waiting list for addiction treatment.

2.3. Patient C

An agitated, 24-year-old man presented to the ED with severe lower abdominal pain and acute urinary retention since two hours. Earlier that day, he had attended a festival where he consumed MDMA and cocaine.

After developing symptoms, he was taken to the festival's emergency tent, where he received 10 mg of oxazepam; however, his condition did not improve. Upon arrival at the ED, a bladder scan revealed 655 mL of fluid retention. Catheterization successfully resolved the retention, though he subsequently experienced stinging suprapubic pain and bladder cramps. He was treated with 2.5 mg oxybutynin, which alleviated his pain. The patient had adequate renal function (eGFR >90 mL/min (CKD-EPI)) and his inflammatory blood parameters were not elevated (CRP 1.9 mg/L, leukocytes 7.7 x10^9/L). Other laboratory results were also within normal limits. Comprehensive toxicological screening using Liquid Chromatography Mass Spectrometry (LC-MS) (Toxtyper™ (Bruker, Bremen, Germany)) of the patient's urine identified the presence of multiple substances, including ketamine, its metabolite norketamine, MDMA, cocaine, benzoylecgonine, cocaethylene, paracetamol, and oxazepam. Despite these interventions, the patient reported persistent urological symptoms such as bladder cramps during a follow-up visit one year later, highlighting potential long-term complications of his substance use.

3. Discussion

3.1. Rising prevalence of ketamine use and associated health risks

Ketamine's increasing prevalence as a recreational drug, particularly in nightlife settings, presents significant challenges for acute healthcare services [5]. Case observations highlight a range of clinical manifestations. For example, Patient A exhibited symptoms typical of the sedative effects of ketamine when combined with alcohol, including unresponsiveness and instability [12,13]. In contrast, Patient B's clinical presentation suggested mixed intoxication, including agitation, apneas, and vomiting, likely due to interactions between ketamine, alcohol, and benzodiazepines, although comprehensive toxicological screening was not conducted [12]. These cases emphasize the importance of awareness in managing complex intoxications.

Currently, ketamine is not routinely included in standard toxicological screenings, which can lead to its frequent omission, even in patients with mixed drug use. The decision to conduct comprehensive toxicological screening remains at the discretion of the emergency physician and is case-dependent. For both Patient A and Patient B, routine toxicological screening did not include ketamine. Its presence was assumed based on self-reporting by the patients and/or accompanying individuals, which should be viewed as an assumption rather than a confirmation of use.

This growing trend in recreational ketamine use, particularly among younger adults, underscores the need for heightened awareness and diagnostic precision when managing ketamine-related intoxications.

3.2. Ketamine-induced uropathy and urological complications

Chronic ketamine use can lead to ketamine-induced uropathy, which is characterized by histological damage to the bladder, resulting in inflammation, fibrosis, and potential renal impairment [18]. Patient C demonstrated both acute and long-term complications. Initially presenting with severe lower abdominal pain and urinary retention, the patient's condition improved following catheterization and pharmacological treatment. However, persistent bladder cramps reported during follow-up suggested a possible progression to ketamine-induced uropathy [12, 13, 19]. Comprehensive toxicological screening confirmed the presence of ketamine, norketamine, and other substances such as MDMA and cocaine.

Symptoms of ketamine-induced uropathy may include acute urinary retention, bladder cramps, pelvic pain, dysuria, and hematuria [18,20]. Additionally, the use of other substances, such as MDMA, may exacerbate urinary retention due to its α-adrenergic stimulation of the internal urethral sphincter, as seen in patient C [19]. These clinical features underscore the complexities of managing mixed intoxications and the importance of recognizing the potential for long-term complications from ketamine use.

3.3. Management of acute ketamine intoxication

The management of acute ketamine intoxication primarily focuses on symptom control and supportive care, with particular emphasis on monitoring respiratory and cardiac function in cases of high-dose ingestion. Given ketamine's short duration of action, long-term observation for mono-intoxications is typically unnecessary [12]. However, in cases where hallucinogenic effects are prominent, placing the patient in a controlled environment with reduced auditory, visual, and social stimuli is essential. Benzodiazepines are commonly used to manage hallucinations or agitation [13]. If these measures are insufficient, anesthetics such as propofol may be considered [13]. Hypertension and tachycardia associated with ketamine intoxication can be treated with benzodiazepines, calcium antagonists, or alpha and beta blockers [12, 13].

In cases of mixed intoxication, the presence of ketamine does not necessarily alter the treatment approach, but it can assist in ruling out other potential causes of clinical symptoms and guide further management, including referrals to specialists or addiction care.

3.4. Management of ketamine-induced uropathy

Ketamine-induced uropathy is a growing concern, particularly among young adults, and requires early intervention to prevent disease progression [18,21]. Patient C's case illustrates the importance of timely identification and treatment of this condition. Immediate cessation of ketamine use is critical in preventing further damage, and pharmacological treatments, such as anti-inflammatory agents (e.g., diclofenac or etoricoxib), may be used depending on the disease stage [18].

The use of anticholinergics such as oxybutynin in ketamine-induced uropathy remains debated, as the condition is primarily driven by inflammation rather than detrusor muscle overactivity [18]. However, in Patient C, oxybutynin was effective in alleviating bladder cramps. The emergence of ketamine addiction clinics and outpatient centers specializing in the prevention and treatment of ketamine-induced uropathy reflects growing awareness of this condition. [22].

3.5. Recommendations for incorporating ketamine in routine toxicological screening

The rising global use of ketamine and its associated health risks highlight the need for its inclusion in routine toxicological screening. As seen in Patient C, the detection of ketamine provides critical information for diagnosing mixed intoxications and guiding treatment decisions. However, ketamine is not routinely included in common drug-of-abuse point-of-care tests (DOA-POCT) for urine screening.

Research supports the incorporation of ketamine detection into toxicological screening, helping identify complications such as ketamine addiction or ketamine-induced uropathy, and improving diagnostic accuracy [23]. Advanced detection technologies, such as comprehensive two-dimensional gas chromatography-flame ionization detection (GC×GC-FID), have proven effective in detecting ketamine and other psychoactive substances [24]. Additionally, techniques like LC-MS/MS and dried blood spot (DBS) sampling offer innovative, low-volume approaches for substance detection, which can provide valuable insights into emerging drug trends [25].

Given the rising prevalence of ketamine use, particularly among younger populations, and its potential for dependence and other health complications, it is crucial to integrate ketamine detection into standard toxicological screenings [26]. By doing so, healthcare providers can enhance diagnostic accuracy, implement timely interventions, and better address the global challenge of ketamine-related health issues.

4. Conclusion

Ketamine's rise as a recreational drug presents significant challenges for healthcare providers, particularly in emergency settings. Its use is often combined with other substances, amplifying its toxic effects and complicating clinical management. Acute ketamine intoxication requires focused symptom treatment, while chronic use can lead to severe long-term complications, such as ketamine-induced uropathy.

Routine toxicological screening often omits ketamine, despite its potential role in diagnosing mixed intoxications and guiding appropriate follow-up care. Integrating ketamine into toxicological screenings will improve diagnostic accuracy, assist in early identification of ketamine-related health issues, and facilitate better treatment outcomes. As ketamine use continues to grow, adopting comprehensive screening protocols and targeted interventions is essential to mitigate its public health burden.

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Femke M. J. Gresnigt: Writing – review & editing, Data curation. **Croes Esther A.:** Writing – review & editing. **Marongiu Sabrina:** Writing – review & editing, Writing – original draft. **van Eijk Maarten:** Writing – review & editing, Conceptualization. **Eric J. F. Franssen:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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