Chapter

An Update of Ketamine Illicit Use

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Abstract

Ketamine is a derivative of phencyclidine with unique anesthetic, analgesic, as well as antidepressant pharmacological properties. Despite its clinical use, ketamine is classified on the list with new psychoactive substances having psychedelic properties. The abuse trend of ketamine increasing globally, and it became a common club drug over the past few decades. Of note, recreational use of ketamine may pose a threat to public health, leading to numerous physical, as well as psychiatric negative effects. In addition, simultaneously or sequentially ketamine use with other drugs, resulting in serious health consequences. Currently, there are no specific treatment options for managing compulsive drug-seeking behavior in patients with ketamine use disorder, while the pharmacotherapy of side effects is limited and mostly symptomatic. In this chapter, we discuss ketamine abuse history. Further, we proposed the mechanisms of neural disinhibition underlying addiction development in ketamine-dependent patients. We have also included details of possible negative consequences focusing on long-term and recreational ketamine use for both, central and peripheral systems. Finally, we provide an overview of ketamine concomitant use and corresponding adverse interactions.

Keywords: ketamine, abuse, club drug, k-hole, k-cramps, ketamine bladder

1. Introduction

Ketamine has long been known as a potent anesthetic drug with analgesic properties, however, it quickly evolved into a recreational drug in the early 1980s [1]. The first use of ketamine as a drug was recorded in 1965 [2]. Widespread, nonmedical uses of ketamine expanded through that time due to sub-cultures began experimented with the drug for mind exploration the inner psyche, and New Age spiritualism.

Ketamine is also known as the 'club drug' and since the mid-1980s, it has been linked to a variety of dance cultures, because of its trance-like state potency. That also explained why teenagers and young adults (16 to 25 years) are the people who are most susceptible to ketamine abuse. Ketamine is known by various names, by clubbers usually called "K", "vitamin K", "super K", or "special K" [3, 4]. In the United States of America as well as in the United Kingdom ketamine was used as an adulterant in methylenedioxy-methamphetamine (MDMA) under the name of "horse pill" [5].

The typical ketamine users are regular visitors of the electronic dance music scene [6]; psychonauts; injecting heroin users, and the 'gay' club/party scene [7]. In addition, according to the data from the Crime Survey for England and Wales (CSEW) for 2012/2013, it is usually single male, aged 20–24, unemployed or studying, and from Chinese or mixed-race ethnic roots [8].

The most important reasons for ketamine's recreational use are as follows: short time to effect; duration of action (up to 3 h), as well as low cost. Ketamine was gained popularity as a party drug due to the appearance of powerful psychoactive effects even at low, subanesthetic (0.1–0.5 mg/kg) doses [9]. As a dissociative anesthetic, ketamine and other drugs such as phencyclidine (PCP) or dextromethorphan (DXM), distort the user's perception of sight and sound, while producing illusions of detachment from the environment or body, known as a „falling into a K-hole" (near-death experience). This state is also associated with the lack of the ability to speak and move around easily, not accompanied by actual loss of consciousness [10]. It is considered that; ketamine had the highest degree of out-of-body experiences among any other drugs, like a bad LSD trip. While not all ketamine users had out-of-body experiences, less than 10% of subjects experience this phenomenon regularly [11]. Of note, these symptoms can be prolonged and even create psychosis associated with schizophrenic and other psychotic disorders. In fact, ketamine has been used experimentally to develop a 'ketamine model' of psychosis [12, 13].

Additionally, hallucinations, emotional withdrawal, and "melting into the surrounding" may occur. It is also very likely for users (at very high doses of ketamine or those combining ketamine with alcohol or other drugs) to experience numbness, amnesia, more intense dissociations, and delirium [14].

Ketamine's ability to induce confusion, amnesia and alter some of the perceptual effects make this drug a so-called "date rape drug". For this reason, ketamine was included in the Drug-Induced Rape Prevention Act of 1966 [15]. Unfortunately, some of the symptoms and side-effects are long-lasting (i.e., impairment to episodic and possibly attentional functioning). Although semantic memory impairments are thought to be reversible as a consequence of ketamine cessation or substantial reduction of its use [9, 16].

2. Epidemiology of ketamine illicit use

The recreational use of ketamine has climbed over decades in the UK [17, 18], Australia [7], Southeast Asian countries such as Taiwan, Malaysia, and China, particularly such phenomenon was reported among the youth and adolescents [19–22]. It could be, in part, due to ketamine's lower status in regulatory systems and lower price, compared to still expensive "ecstasy" or methamphetamine. In Hong Kong, where ketamine was classified as a Schedule I drug since 2000, ketamine became the most commonly misused drug in the early 2000s [21].

The abuse of ketamine has been declining over the past years but is still relatively common. According to the national survey-based 'Monitoring the Future Study' in the United States ketamine ingestion decreased between 2002 and 2012 from 2.5% to 1.5%, and from 1.3% to 0.4%, among 12th graders and college students, respectively [23].

The decreasing ketamine popularity was also noticed in the United Kingdom (UK), where it has been classified on the list as a Class C drug since 2006 [21], and then was reclassified as a Class B drug from 10 June 2014 [24]. The World Health Organization fact file has demonstrated the ketamine usage in the UK decreased from 0.6% to 0.4% and from 1.8% to 0.8%, respectively, between 2011 and 2013 [23]. Similarly, in another study the level was continued to fall in 2013 to 50.6% and 31.5%, but these were still higher than for US respondents (26.3% and 15.4%, respectively) [25].

Before the COVID-19 pandemic global last year use rates of ketamine were 6.72% in 2016, 8.6% in 2017 and 6.5% in 2018; lifetime rates for 2017 and 2018 were 11.7% and 10.4%, respectively [26, 27]. During the COVID-19 pandemic state, a reduction in 'party drugs'-like ketamine consumption was expected. As the

limited access to pubs, clubs, and festivals cancelation were the primary reasons for decreases in the recreational use of illicit drugs which are typically linked to the nightlife and party scenes. In fact, in Australia, the use of ecstasy/MDMA and related drugs (e.g., cocaine, ketamine) had fallen compared to the pre-pandemic level [28, 29]. The less interest in club drugs like ketamine was also noticed by Neutravel, an Italian non-governmental organization (NGO) [30].

Surprisingly, in the U.S. according to the national survey-based 'Monitoring the Future Study', it has been demonstrated the ketamine use raised between 2019 and 2020 from 0.7 to 1.3% respectively among 12th graders [31]. Some individuals paradoxically start to use ketamine due to anxiety caused by the pandemic time, while others increased its consumption during lockdown spent at home. [32].

3. Ketamine status in the regulatory systems

In 1999, ketamine including its salts, isomers, become a Schedule II non-narcotic substance under the Federal Controlled Substances Act in the U.S. This means that the drug does have lower misuse potential but is still approved for use in hospitals and other medical settings as an anesthetic. Because of this, it is illegal to possess ketamine without a medical reason, prescription, or as a part of the research. Thus, the illicit use of ketamine appears to be from illegal diversion from legal prescription, but analogs which usually contain a range of undeclared psychoactive substances (i.e., amphetamine, benzocaine, cocaine, MDMA, methoxetamine, paracetamol, piperazines, and synthetic cathinones) may also be found on the streets [33].

Nowadays, in the U.S., ketamine is classified as a schedule III drug under the DEA Controlled Substances Act. Medications in this category are often used for pain control, or anesthesia, or appetite suppression. It means that ketamine has less potential for abuse than Schedule I (heroin) or Schedule II (cocaine) drug, and it is not as tightly regulated as most opioids. However, abuse of Schedule III substances may lead to moderate or low physical dependence but more commonly leads to high psychological dependence. This means that for users outside the approved limits, its adverse mental and physical health effects can be hazardous [34].

Ketamine has been revived a couple of times in 2003, 2006, and 2012 by The Expert Committee on Drug Dependence of the World Health Organization (WHO), and finally, it has remained on the list as an essential medicine. The experts considered that the international control is not appropriate in this case, as new facts about ketamine were not sufficient to warrant scheduling. In the recent World Drug Report by United Nations Office on Drugs Control 2019 (UNOD 2019) [35], ketamine is classified under new psychoactive substances (NPSs), which are not under the control of international drug conventions, but which may pose a threat to public health. Since 2000, in the European Union, ketamine is not under the control, however further monitoring of drug use is recommended by the European Commission. Despite the increasing trends of abuse, dependence, and dying from ketamine recreational use, its status did not change significantly over time. It seems to be still relatively low, especially when compared with other Novel Psychoactive Substances (i.e., synthetic cannabinoids and cathinones or 'designer benzos'). This raises important concerns about the underestimation of ketamine.

4. Methods of ketamine abuse

The route of ketamine administration is crucial for the type and the intensity of the experience the effect. Ketamine has a dose–response curve with variable effects

Dose range [mg]	Related effects
Low: 10–75	mild euphoria, feeling of well-being, feelings of calmness and relaxation, empathy, smell, and tastes muted, visual hallucinations, enhanced color vision, sense of touch deterioration
Medium: 60–125	slow motion, auditory hallucinations (ringing in the ears), detached feeling from the body, loss of coordination, diminished reflexes
High: 100–250	felling light, timelessness, body dysmorphia, 'K-hole' out-of-body experiences

Table 1.
The common effects of ketamine in snorted doses.

Single dose [mg]*	Route	Onset of action [min]	Duration of action [min]
75–125	i.m.	1–5	30–45
60–250	i.n.	5–10	45–60
50–100	i.v.	seconds	30–45
200–300	p.o.	15–20	60–120

*Abbreviations: intramuscular (i.m.); insufflation, intranasal or "snorting" (i.n.); intravenously (i.v.), per os, orally "by mouth" (p.o). *Typical recreational dose is 10–25% of the effective general anesthetic dose [37].*

Table 2.
Ketamine recreational dose ranges, the routes of administration, onset and duration of action ([36] with some modifications).

(**Table 1**). However, unlike other psychedelic drugs like LSD, ketamine triggers a short trip, lasting no more than 1.5 hours. The illicit product mostly involves evaporating the liquid from the diverted injectable solution to produce a dry powder that is formed into tablets or sold as a powder. The most common method of ketamine abuse is "snorting" and 96% of ketamine users choose such a way for its usefulness and rapid action noticed in roughly 5 to 10 minutes [33]. In comparison, oral consumption requires between 15 and 20 minutes (**Table 2**) [25]. For nonmedical use, a typical intranasal dose is 50 mg and the oral dose is 100 mg [38, 39], but the usual recreational dose range between 60 and 250 mg of ketamine [40]. Ketamine abusers will often self-administer several sequential doses of the drug to maintain psychotropic effects over time. However, an injection results in the most rapid effect (within seconds to minutes), though such a way of administration is quite difficult especially in clubs. Interestingly, a recent animal study has revealed that a high IV ketamine dose caused the complete cessation of cortical EEG activity for several minutes, similarly to the 'K-hole' in humans [41]. Recently, online user fora, as well as research findings, also support vaping as a possible route of ketamine administration [42, 43].

5. The central and peripheral consequences of long-term and recreational ketamine misuse

There are no medical uses in which ketamine is provided chronically. The majority of reported long-term effects of ketamine are those which have developed in chronic recreational users or animals during preclinical studies. Although controlled human studies of repeated doses of ketamine are prohibited because it would be unethical to give an anesthetic with pronounced adverse effects more often. In clinical settings, ketamine is rather well tolerated. Although the pattern of

adverse effects of non-medical ketamine use may differ from that expected from prescribed medical use. In individuals who misuse ketamine, serious sequelae, including prolonged neuro-, urological-, and gastro-toxicity may occur. The residual effects which may persist beyond acute ketamine dosing and its long-term consequences have been compiled and presented in the following subsections below.

5.1 Psychosis

Evidence of the psychotogenic potency of ketamine initially emerged from general anesthetic use where clinicians noted drug- related post-anesthetic reactions (i.e., confusion, vivid dreams, and hallucinations) leading to a reduction in the clinical drug utility [9, 44, 45].

There are some evidences that infrequent and frequent ketamine users exhibited higher levels of schizophrenia-like, dissociative, and depressive symptoms [13]. Hansen et al. [46] described the most common subjective effects of ketamine in recreational users including the sensation of light through the body; novel experiences concerning "body consistency" (e.g., being made of wood, rubber, or plastic); unreal shape or size of body parts; a sensation of floating or hovering in a weightless condition; timeless; sudden insight into the self; the experience of being at one with the universe; an experience of leaving the body; visions and hallucinations).

Subanesthetic doses of ketamine in healthy volunteers also trigger positive and negative schizophrenic-like symptoms as well as perceptual alterations similar to dissociative states with altered body perception, depersonalization, derealization, and distorted sensory perception. Of note, ketamine had the highest degree of out-of-body experiences compared to the other drugs as was mentioned in the previous section. While it is given to chronic, stable schizophrenics, ketamine has been shown to cause a re-emergence of the acute phase of the illness [47].

Ketamine exerts its unique behavioral effects mostly by blocking the NMDA receptors [48, 49]. Although phencyclidine (PCP; "angel dust") has a 10-fold greater affinity for the NMDA receptor and is more excitotoxic than ketamine. Over the past several decades many animal models have been developed using drug mimics endogenous deficits in NMDA receptor function to study the mechanism of schizophrenia [48]. The cumulative effect of repeatedly using ketamine and/or a residual effect has occurred 3 days after abusers took this drug [50]. More importantly, even strong schizophrenic-type symptoms and perceptual distortions may persist after cessation of ketamine use [17, 36].

One of the explanations of such effect is NMDA receptor dysfunction even several days after acute use. Second, a residual effect may also be psychological in that ketamine produces an intensely subjective experience that could affect users' perceptions of the world for several days after it is taken [13, 50].

5.2 Cognitive deficits

There is increasing evidence that regular and long-lasting ketamine use can induce central nervous system depression and impair cognition, in particular visual and verbal memory as well as executive function [50–52]. The frequent ketamine users with increasing drug doses were more likely to have cognitive deficits, especially with short- and long-term spatial working memory and pattern recognition memory tasks [53]. Short-term memory and visual memory deficits occur usually in users who abused the drug at least 4 days per week. Similarly, according to findings from animal studies, ketamine seems to deteriorate memory at relatively high doses. Short-term memory and spatial memory were impaired in rats administered 30 mg/kg i.p.

and were revealed by the delayed spatial alternation task and finding to the hidden platform in the Morris water maze test [54, 55].

Interestingly, ketamine appears to have greater potency to reduce cognition than other drugs of abuse [13]. These cognitive deficits may affect functioning in the abuser's daily life due to difficulty in remembering conversations and other people's names [13]. It has been also found that men to be more affected by these effects than women [56]. In addition, cognitive deficits are also related to the impairment of the psychomotor performance, such as coordination, balance, and hand-eye movements. This lack of coordination may cause the inability to drive or operate machinery, thereby increasing accidental injury or even mortality from motor vehicle collisions. Data from an epidemiological study involving drug-related motor vehicle collision fatalities found 9% related to ketamine use, representing a disproportionate number of fatalities compared to alcohol and opioid misuse [57].

In 2007, according to data from a single trauma centre in Hong Kong roughly 4.5% of drivers involved in non-fatal crashes tested positive for ketamine [58].

In addition, ketamine may gradually change the brain's chemical system affecting opioids, dopamine (it activates dopamine systems), serotonin, noradrenaline, nitric oxide, sigma, GABA (gamma amino-butyric acid), and acetylcholine, among others [59, 60].

Ketamine has been also induced electrophysiological dissociation between the thalamo-neocortical and limbic systems and potentiated the synaptic inhibition of GABA [36, 61, 62]. However, the key pharmacological mechanisms underlying ketamine-related cognitive deficits are mediated via an NMDA glutamate receptors hypofunction [4]. There have been also shown that NMDA antagonists' potency induced degeneration in a subset of limbic structures like those which are altered in patients with psychoses [63]. Animal studies revealed that direct apoptotic neurodegeneration was induced by NMDA-R antagonists, including ketamine, in the developing rodent brain. However, this ketamine effect was more evident in older rats [64]. According to other findings from animal studies the racemic ketamine (with its preservative benzethonium chloride) and S-ketamine have been associated with neuronal apoptosis and sensorineural consequence following high dose and/or long-term i.v. administration [65–68]. However, translatability to humans is questioned and the impact of lower subanesthetic doses is uncertain.

In this way, ketamine abuse may display structural damage in multiple brain areas, such as the frontal, occipital, parietal, limbic, and corpus striatum [69, 70].

There have been shown that such detrimental effect is related to time and the dose of ketamine abuse [69]. Data have also revealed that the brain atrophies may occur within 1 year of ketamine intensive use with expected further progression in the following years [70]. In fact, ketamine dose reduction may restore cognition, but we cannot rule out irreversible and residual effects [17, 50].

As data have demonstrated NMDA receptors must be blocked for at least 24 hours to produce irreversible effect or death in the cells, but ketamine has a short half-life (about 20 minutes in rats) thus many injections are needed, over a prolonged period, to produce persistent change [71].

Although we have still limited data regarding cognitive ability from the ketamine ex-user population to provide straightforward conclusions for these findings. To date, there is no specific pharmacotherapy to avoid cognitive deficits in long-term ketamine use. The management of these problems is largely supportive and symptomatic. The cognitive enhancers are taken into consideration, such as modafinil, commonly used in stimulant addiction, as well as cholinesterase inhibitors (i.e., rivastigmine, donepezil, galantamine) usually recommended in other disorders with cognitive impairments (i.e., Alzheimer's disease, Parkinson's disease, traumatic brain injury, and schizophrenia), among others [51, 72].

5.3 Pro-depressant effect

Compared to growing evidence available for the anti-depressant effect of ketamine, there is still less for its pro-depressant potency [73]. Ironically, an intranasal ketamine formulation was recently approved in the USA, and Europe to treat intractable depression and acute suicidal ideation [74]. The depressive potency of ketamine seems to be dose and time-related. Insights from the animal study indicate that the antidepressant action at a dose of 10 mg/kg was not observed in rats receiving a higher dose of ketamine (80 mg/kg) [75]. Likewise, the anti-depressive effects linked to the subanesthetic ketamine dose (0.5 mg/kg) might not correspond to the same effect at the dosages range, preferred by recreational users. It was suggested that an opposite pro-depressant effect may be linked to certain neuroadaptation changes [76]. In fact, some studies demonstrated that chronic use of ketamine causes more lasting depressive effects [4, 36, 53]. There have been shown that ketamine abusers reported depressive symptoms quite common, roughly 72.5%–77.5% of them were diagnosed with moderate to severe depression based on the Beck Depression Inventory scores [77, 78].

According to the results from various studies, the prevalence of major depressive disorder (MDD) in outpatient settings fluctuating between 7.8–18.5%, in comparison to inpatient populations with nearly one-fourth (23.3%) ketamine-dependent MDD comorbidity [79–81]. Though, according to certain authors, the mood measures revealed little and clinically insignificant difference between groups with slightly higher scores in the ketamine users [50].

Interestingly, increased depression scores have been found in both daily users and ex-users in a longitudinal study, although not more infrequent users [53]. The mechanism of the acute antidepressant and chronic depressant effects may be linked, but it is unclear exactly how this opposite effect is mediated. Why abstinent ketamine users were more depressed is also less clear but may be linked with a change in their lifestyle. In fact, the frequent ketamine users had experienced more negative life events over the 12 months, due probably to their chaotic lifestyles, which may also trigger depressive symptoms [82].

In addition, previous evidence indicates that the depressive symptoms in ketamine users may persist even for 1 year after abstinence [53]. Furthermore, increased depression in frequent users could also reflect their increased dependency on ketamine, as depression is also commonly comorbid in opiate- and alcohol-dependent populations [83, 84]. Recent data imply that depression might be associated with craving (stronger propensity to administer more ketamine). There have been shown that patients with higher craving intensity demonstrated a greater severity of depression, longer history of ketamine administration, and greater use frequency than those with lower craving intensity [81].

5.4 Tolerance

Ketamine-induced tolerance may be considered in many aspects, although it is exceptionally mentioned in psychopharmacological clinical studies.

Firstly, ketamine is known as an effective anesthetic drug widely used in the clinic, however, as with many drugs, this effectiveness is often compromised due to tolerance to ketamine's anesthetic effects, which might be of great importance especially when the patient has a history of drug abuse. Similarly, there are several papers indicating tolerance to the antidepressive effects of ketamine during repeated administrations [85]. Nonetheless, tolerance to ketamine can develop rapidly in all species, including after one large dose [86, 87], or even in patients with major depressive disorder. A great example derived from the case study of

Bonnet [85] provided evidence that a continuous antidepressant response to daily ketamine injections can be followed by a swift return of a major depressive episode after cessation of ketamine. Other papers demonstrate animals chronically given ketamine that required increased doses of ketamine to reach the target anesthetic plane. Moreover, animals had a shorter duration of anesthesia [86, 88]. Surprisingly, rats pretreated with intraperitoneal morphine at a dose of 5.6 mg/kg demonstrated cross-tolerance to ketamine's anesthetic effects [88].

5.5 Withdrawal

Ketamine, being a drug easily abused, may induce several uncomfortable adverse reactions as a consequence of its cessation. There is increasing evidence that ketamine causes psychological but not physical dependence. Withdrawal symptoms are usually like withdrawal from cocaine with very strong cravings. Symptoms of acute withdrawal may be short-lived and not identified as such [89]. However, the withdrawal from ketamine may paradoxically cause depression [90]. Other withdrawal symptoms after ketamine discontinuation include dysphoria, shaking, sweating, palpitations, tiredness, low appetite, low mood, chills, autonomic arousal, lacrimation, restlessness, anxiety, nightmares, paranoia, delusions, and hallucinations [81, 91, 92]. Noteworthy, these withdrawal symptoms typically begin within 24 h of discontinuation and last approximately 3 days, although in some cases, they may persist for 2 weeks and thereafter stabilize [93].

Apart from the abovementioned, there several reports are indicating that due to ketamine discontinuing mild forms of schizophrenic-like symptoms occur [17].

5.6 Ketamine-induced uropathy: "the ketamine bladder"

Recreational abuse of ketamine has been associated with bladder pain syndrome; ulcerative cystitis also known as 'ketamine bladder'. Up to a quarter of ketamine, abusers may experience such problems. According to the European Medicines Agency (EMA) and the UK Yellow Card Scheme pharmacovigilance database about 23% and 17% of ketamine-related adverse drug reactions (ADR) respectively referred to renal/urinary disorders. Interestingly, such issues being more common among women than men [94]. In general, urological problems occur within 1 month-1 year time frame following the start of ketamine use, but recent pharmacovigilance data revealed that even an acute ketamine administration may be associated with urological risks, as in some cases the risk was noticed within 48 hours of treatment [94].

Initially, ketamine associate bladder disturbance may mimic common conditions such as urine infections and it may be difficult to diagnose, but further urinary symptoms may substantially disturb the quality of the abuser's life thus extreme individuals have difficulty with passing urine. There are reports of needing to pass urine up to 20 times an hour, leading to hydronephrosis and finally kidney failure [4].

Damage to the urinary barrier initiates bladder pain and, in ketamine-induced cystitis, loss of urothelium from large areas of the bladder wall was reported [95]. Ketamine abuse also induces small bladder volume, bladder wall thickening, and mucosal enhancement. The most common ketamine bladder symptoms reported in the 2018 Global Drug Survey were as follows: urine frequency 38%; pain in the abdomen 25%; burning when urinating 18%; incontinence 7%; and blood 3% [96].

The first report of the urological syndrome was published in 2007 by Shahani and colleagues [97]. The cause of urinary toxicity appears to be multifactorial and not fully explained. It is postulated that the direct toxic effect of ketamine or its

active metabolite (norketamine) on the urinary tract may play a crucial role [98]. It is also pointed out, that the urinary toxicity seems to be unrelated to ketamine interaction with NMDA receptors (NMDAR). Thus, in vitro studies revealed that normally human urothelial cells were unresponsive to NMDAR agonists or antagonists, and no expression of NMDAR transcript was detected [95].

A recent study offers new evidence for a mechanism of direct toxicity of ketamine to the urothelial by activating the intrinsic apoptotic pathway. In fact, exposure to ketamine in noncytotoxic concentrations initiates the transient release of calcium Ca(2+) from the endoplasmic reticulum into the cytosol. However, ketamine concentrations >1 mmol/L become cytotoxic and provokes a larger-amplitude increase in cytosolic Ca(2+) concentration. Consequently, sustained elevation in Ca(2+) leads to pathological mitochondrial oxygen consumption and ATP deficiency, and it initiates damage to the urinary barrier [95].

The chronic immune response of the bladder interstitial cells may be another possible underlying mechanism of toxicity [99, 100]. Biopsies have also revealed epithelial denudation, eosinophilic, as well as mast cell infiltration [97, 101]. Ketamine may also trigger interstitial fibrosis by damaging the papillary medullary interstitial cells [98]. There are also reports of metaplasia in the intestine related to ketamine abuse [102]. Furthermore, ketamine through its central action may disturb the contractile response of smooth muscle from appropriate stimuli [103].

In addition, ketamine may induce highly destructive microvascular changes causing epithelial-to-mesenchymal transition, which finally contributes to bladder or kidney fibrogenesis [100, 104].

Compared to the urinary tract, renal damage and bilateral hydronephrosis are less frequent but may also occur. Chronic kidney failure may develop as the final consequence of a long-term sequel [105].

Of note, there a no specific and casual pharmacotherapy for ketamine-related urinary tract disorder. The symptomatic treatment with antibiotics, anti-inflammatory agents, steroids, and anticholinergics in most cases has failed [106]. In such a scenario, the second line of alternative treatment with intravesical agents such as hyaluronic acid, and injections of Botulinum toxin-A should be considered. Preclinical studies have also suggested a future therapy with combined intravesical liposomal onabotulinum toxin-A instillation and mesenchymal stem cells placed directly into the bladder submucosal layer [107]. However, the urinary problems may improve and became reversible if ketamine use is reduced/withdrawn, thus ketamine abstinence should be the first step in ketamine-induced uropathy treatment. The abstinence greater than 3 months is related to some improvement and less severe symptoms. Of note, in some cases, urological issues may persist for up to 1 year after ketamine abstinence [108]. More invasive methods, such as a catheter (tube into the bladder), urinary diversion, and nephrectomy may be required in the prolonged ketamine abuse and irreversible renal damage which may produce a burden to healthcare resources [100, 102, 103].

5.7 Gastrointestinal pathology: 'K cramps'

Regular and long-term ketamine use is associated with gastric pathology of unknown etiology, colloquially termed 'KCramps' [37, 98].

In line with the 2010 *Mixmag* Survey, 'K cramps' occurred in 30% of ketamine users and was a more common issue among women [109]. The persistent epigastric pain is classified as the commonest upper GI symptoms as was presented in 73% of abusers after a higher dose, daily ketamine use [110]. Among symptoms that were also frequently diagnosed in ketamine users are cystic dilatations of the common bile duct, in association with abnormal liver function tests [111–113].

In a retrospective study of GI symptoms followed by inhalational ketamine use, 28/37 of the subjects experienced upper GI symptoms. The mean time of ketamine use was 4 years before admission. Exclusion criteria included potential risk factors and a history of GI disorder. The most common finding was epigastric pain only, which occurred in 23 (62.2%) users. Four users had epigastric pain with vomiting. In sporadic cases, gastroduodenitis, and intestinal metaplasia have occurred. More importantly, all symptoms relief with abstinence from ketamine use [110]. Of note, pains symptomatology related to GI in ketamine users may resemble irritable bowel syndrome as in some parts tend to be triggered by psychological changes [37, 114].

There has been shown that gastric pathology among ketamine users correlated with the duration of drug use [111, 115]. The exact mechanism by which ketamine produces cholestasis and biliary dilation is unclear but is a possible direct link to NMDA receptor blockade in smooth muscle. In addition, ketamine may also act through the dorsal motor nucleus of the vagus, projecting to the gall bladder [116].

Effective treatment of GI toxicity includes discontinuation of ketamine use which can lead to the relief of symptoms, otherwise, treatment options are nonspecific [110].

Of note, there are certain cases of evidence of causal risk between chronic ketamine use and GI toxicity as dilated common bile duct regressed with abstinence but recurred following a return to ketamine use [111].

6. Ketamine and other substances/drugs adverse reactions

The phenomenon of interaction is used in clinical practice as multi-drug therapy. Its aim is to increase the pharmacological potency and obtain desired therapeutic effect while reducing doses of individual drugs. Such steps reduce the likelihood of side effects and are beneficial for the patient. However, the problem arises when unwanted drug interactions occur, and this includes i) pharmaceutical interactions, i.e. incompatibilities arising outside the patient's body; ii) pharmacokinetic interactions related to the fate of the drug in the body at the stage of its absorption, distribution, metabolism and excretion; and finally iii) pharmacodynamic interactions, where one drug modifies the action of another drug.

All these benefits as well as undesired interactions are true for ketamine and other substances. Use with multiple drugs has been fatal.

Firstly, ketamine (both its R(−)- and S(+)-enantiomers) undergoes hepatic biotransformation through the cytochrome P450 (CYP450), particularly with the involvement of CYP2B6 and CYP3A4, to form norketamine. Therefore, an alteration of CYP450 metabolism results in clinically significant drug–drug interactions that can further cause unanticipated adverse reactions and/or therapeutic failures. For instance, drugs that induce both these cytochrome isoforms may reduce exposure to ketamine. In contrast, substances inhibiting CYP enzymes can lead to an increase the exposure to the drug. As a great example is the treatment with diazepam, being a substrate of CYP3A4, which increases ketamine plasma half-life, thus its sedative effects [117, 118]. On the other hand, ketamine can also influence diazepam metabolism as its decreases CYP3A4 enzyme activity [119].

Apart from the involvement of CYP 450 isoforms in the metabolism of ketamine, also another hepatic phase II enzymes may be taken under consideration. Indeed, ketamine has been shown to inhibit UGT2B7 and thus the metabolism of morphine both in vitro and in vivo [120, 121], therefore increases the liver concentration of the opioid. Intriguingly, also the brain concentration of morphine is found to increased (three- to five-fold 90 min after administration). However, such drug concentration changes in the brain are not because of changes at the

blood–brain barrier as it was compared with oxycodone mainly metabolized by cytochrome P450 (CYP) enzymes [122]. Also, when considered oppositely, morphine, but not oxycodone, pretreatment increased the brain and serum concentrations of ketamine [123].

CYP3A4 enzyme is known to be affected by compounds derived from grapefruit juice or whole fruit (i.e., furanocoumarins and, to a lesser extent, flavonoids) [124]. Therefore, in the case of ketamine given orally, a significant increase in plasma concentration can be found in healthy volunteers [125].

Unfortunately, drug metabolism via CYP450 enzymes exhibits also genetic variability (polymorphism), thus in this case also some variations in the exposure to ketamine are obvious. Poor metabolizers of enzymes metabolizing ketamine are extremely rare. However, the paper of Rao et al. [126] provided with information that CYP2B6*6 polymorphism variant did not affect single, low-dose ketamine metabolism, clearance, and pharmacokinetics in healthy human volunteers, though diminished ketamine metabolism in vitro.

Concerning pharmacodynamic interaction once should be said that the nature of ketamine-drug interactions together with the observable effect is highly dependent on the drug type and thus the molecular target (i.e., opioidergic system, dopaminergic, serotoninergic, etc.) as well as from the dose used. There is a great several papers characterizing possible pharmacodynamics interactions between ketamine and different drugs both natural and synthetic. For instance, estrogen together with progesterone potentiated ketamine-induced antidepressant effect [127], while BNN27, a synthetic derivative of dehydroepiandrosterone reduced ketamine-induced ataxia [128]. Ketamine was found to produce additive effects when combined with gamma-aminobutyric acid (GABA) activity. This was found true for barbiturates such as thiopental at a hypnotic endpoint [129], but not with a benzodiazepine - midazolam [130]. Also, for anesthesia induction, the combination of ketamine and midazolam was found additive rather than synergistic at the endpoint of loss of response to verbal command [130]. When introduced with other benzodiazepines (i.e., clonazepam, alprazolam, lorazepam), specifically for the treatment of long-lasting depression, as well as considering that both types of drugs act on interneurons, ketamine antidepressant efficacy was mute [131, 132]. This finding suggested that benzodiazepines inhibitory activity towards ketamine's antidepressant effect may be related to attenuation of neuroplastic processes, emerging subsequently after the acute effect and after ketamine and its active metabolites are eliminated from the blood since benzodiazepines occurred ineffective in the first 24 h post-concomitant administration of both drugs [131].

Analyzing other effects mediated by simultaneous ketamine and benzodiazepines, the following can be mentioned: (1) inhibition of ketamine-induced hyperlocomotion by diazepam [133]; (2) ketamine's emotional stress reduction by a sub-hypnotic lorazepam [134]; (3) lorazepam intensification of ketamine sedative effects [134]; (4) potentiation of ketamine amnestic action by diazepam and lorazepam [134, 135]; (5) antagonism of the cardiovascular effects of ketamine by diazepam [136], or (6) ketamine-induced emergence delirium prevented by midazolam [137]. Whereas concerning antipsychotics such as haloperidol it has been shown that it can reduce ketamine-induced cognitive impairment. In addition, haloperidol was found to attenuate the increase of locomotor activity and stereotyped behavior, reversed the motor incoordination, and blocked the hypermobility induced by acute administration of ketamine in rodents [138].

Yet another possible interaction occurs between ketamine and the opioid system, as ketamine (in particular (S)-ketamine) was characterized as a drug that partially interacts with the opioid system, particularly mu-opioid receptors [139]. Indeed, as already mentioned, ketamine enhances levels of morphine, which may

explain the long-lasting morphine-induced antinociception [120]. Importantly, the enhanced level of morphine is strictly associated with ketamine inhibitory activity towards morphine tolerance, which is mainly by N-methyl-d-aspartate (NMDA) receptor antagonism [121, 140]. On the other hand, it has long been suggested that opioids may enhance the antidepressant effect induced by ketamine, as naltrexone attenuated this activity [141]. However, currently, the involvement of the opioid system in this specific action is unclear since partial agonists (i.e., methadone and buprenorphine) did not influence ketamine's antidepressant effect [142].

Opioids are well known for their great ability to induce respiratory depression, especially when overdosed. Intriguingly, also in this aspect, an interaction between ketamine and opioids exists. In fact, intraperitoneal (i.p.) administration of ketamine has led to significant respiratory depression in mice, but not in mu-opioid receptor knock-out mice [143].

As with other CNS medications, it should be mentioned that ketamine is capable of modifying effects mediated by alcohol consumption and illicit drugs. In the first case, it has been revealed that subjects simultaneously taking alcohol and ketamine are more vulnerable to suffer from the urinary tract and gastrointestinal problems such as pain with urination, increased frequency of urination, or even lower abdominal pain [144]. Of note, individuals with a family history of alcoholism with altered NMDA activity may have a blunted effect on the negative psychological reactions to ketamine. Whereas, as a great example of a drug of abuse, apart from the aforementioned opioids, for which a concomitant use with ketamine may result in unpredictable and extremely dangerous side effects is a so-called "liquid Extasy" [92, 145]. This compound is a gamma-hydroxybutyric acid (GHB), being a naturally occurring analog of gamma-aminobutyric acid (GABA), with esthetic and euphoric properties. Concerning ketamine, it has been shown that this drug together with GHB, in particularly high doses, results in an increased risk of respiratory depression and fatality. In addition, ketamine produced and enhanced GHB-mediated cataleptic effects in mice [146]. Also, can lead to a significant increase in sleep time.

Dangerous interactions were also noted for ketamine and methamphetamine both in vitro and in vivo. In fact, the co-exposure of these two drugs resulted in significant cytotoxicity and synergy on oxidative stress in HepG2 cells [147]. While in mice treated with a low dose of methamphetamine and ketamine, the stress-related depressive and anxiety-related behavioral alterations caused by the psychostimulant were antagonized consistently by both high and low doses of ketamine [148]. Furthermore, a combined repeated administration of both drugs was reported to increase significantly the risk of psychological dependence as shown in a rat conditioned place preference test [149]. In turn, in methamphetamine-dependent humans, a very high prevalence of psychotic disorders was suggested for those who occasionally or continuously use ketamine [150]. Moreover, when used with other stimulant drugs such as ecstasy, high blood pressure may appear [50]. Ketamine may be also toxic when is combined with caffeine. Theoretically, this may be a concern in people who have consumed energy drinks, especially at nightclubs where ketamine may be abused.

Ketamine is also a very popular drug taken together with cocaine. Unfortunately, such a combination occurred to result in a potentiation of cocaine-induced hepatotoxicity associated with sub-massive hepatic necrosis. These observations were indicated for rats pretreated with ketamine for three consecutive days at a dose of 100 mg/kg with a single dose of cocaine (5 mg/kg, i.v.) [151]. This information is especially intriguing when compared with recent data demonstrated that a single ketamine infusion in cocaine abusers, coupled with a mindfulness behavioral modification program, seems to be a promise to achieve both the abstinence and reduction of the risk of relapse [152].

Ketamine is known to be related to several molecular targets, either directly or indirectly. Indeed, due to its interactions with sodium channels (local anesthetic properties), i.e. L-type calcium channels and potassium channels [153], ketamine when administered with grapefruit juice may cause harmful effects ranging from relatively mild hypotension and dizziness. Furthermore, ketamine being an antagonist towards acetylcholinergic receptors produces various effects while interacting with cholinesterase and anticholinesterase agents. One great example is the interaction with atropine which was found to slightly increase the ketamine-induced time of immobility in rats [154]. On the other hand, ketamine blocked the EEG and the behavioral toxic effects of neostigmine and physostigmine. While physostigmine can reverse the central anticholinergic effects and also antagonize ketamine hypnotic effects [155]. However, in the aspect of somnolence reverse, there are contradictory results. In fact, while Balmer [156] found physostigmine effective in reversing ketamine-induced somnolence. Drummond et al. [157] indicated physostigmine as ineffective in producing a rapid patient awaking or even in reducing hallucinatory behavior.

Another possible cellular target of ketamine includes the monoaminergic system, particularly noradrenergic and serotonergic. Alpha2 agonists such as xylazine or medetomidine as well as dexmedetomidine were found safe when combining with ketamine [158]. Both these drugs were shown to reduce the dosage of ketamine and the occurrence of psychomotor symptoms after ketamine. As for compounds actin at serotonergic receptors of various types or being selective serotonin reuptake inhibitors (SSRIs) it can be provided that repeated subanaesthetic doses of ketamine can redeem the time lag for the antidepressant-like effects of citalopram [159]. Also, such a combination given to rats resulted in a decrease in the immobility time and increase in struggle time in the Forced Swim Test (FST) and Tail Suspension Test (TST) as compared to control group [160].

Beneficial effects were also observed for other serotonergic agents. For instance, intravenous ketamine emetic properties were inhibited by ondasteron in children [161]. Moreover, ketamine was reported to potentiate the anxiolytic effects of SSRIs such as fluoxetine [162].

Apart from the above-mentioned, also cannabinoids were indicated to be vulnerable to interact with ketamine. These includes delta 9-tetrahydrocannabinol being the major psychoactive molecule among synthetic cannabinoid ligands that act at cannabinoid 1 receptor (CB1), as well as cannabidiol (CBD) displaying potency as an antagonist of CB1 and CB1 receptor agonist, respetively. Indeed, Frizza et al. [163] reported 9-tetrahydrocannabinol to prolong the anesthesia induced by ketamine in mice. Whereas CBD was found reduced depersonalization when administered with ketamine, as measured by the Clinical Administered Dissociative State Scale in healthy humans [164].

Overall, it can be noted that ketamine, possibly due to the complex mechanism of action, may interact with various molecular targets resulting in both critical and beneficial effects. Therefore, there is no unequivocal opinion as to whether ketamine should be used with caution or not; this depends strictly on the type of the second drug used as well as on other physiological and pathophysiological factors, including age, genetic polymorphism, and occurrence of diseases and disorders.

7. Conclusions

Non-medical, recreational use of ketamine has increased in certain populations/sub-groups with geographical variations in its use patterns. Ketamine abuse seems to be an important public health challenge due to its association with multiple

physical and psychological harms. Noteworthy, the psychedelic effect may have a therapeutic value in some points and be harmful in others. Long term users may develop different neurobiological alterations, psychological dependency, withdrawal, tolerance, schizophrenia-type symptoms, poor psychological well-being, memory difficulties, and finally worse quality of daily life. In the long-term use, there is also evidence of deleterious effects for the peripheral system, associated with serious lower urinary tract symptoms, and gastrointestinal pathology. In addition, polysubstance consumption is inherently risky and can lead to serious adverse consequences, especially when abusers mixing ketamine with eighter depressants or stimulants. Although of concern did not cause any significant changes in ketamine's legal status over the years. There are numerous studies revealed the effects of a single administration of ketamine, thus the effects following repeated use and long-term consequences are still less known and underestimated. More study is needed to better elucidate the real ketamine safety profile regarding both its long-term recreational use and its clinically use as an antidepressant agent.

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Conflict of interest

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