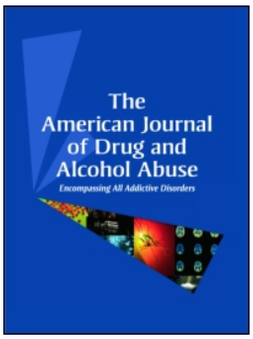

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REVIEW

Overdoses and deaths related to the use of ketamine and its analogues: a systematic review

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ABSTRACT

Background: Although the misuse of ketamine constitutes a worldwide issue, ketamine is quickly taking its place as a therapeutic option in the management of several mental disorders. However, the use of ketamine and/or its analogues, as well as combinations with other drugs, can be fatal.

Objective: To outline the cases of overdoses and deaths related to the use of ketamine and/or its analogues, as reported in the scientific literature. To investigate if ketamine is safe in a therapeutic context, particularly in its use as an antidepressant.

Methods: Electronic searches were performed on three medical databases. Articles describing cases of overdose and/or death associated with ketamine and/or its analogues were included. After the removal of duplicates, title analysis and full-text analysis, 34 articles were included in this review.

Results: Eighteen articles described fatal cases and sixteen described overdoses. Poly-substance use was mentioned in 53% of the selected articles. Most cases were males and the ages varied from two to 65 years old. A total of 312 overdose cases and 138 deaths were reported. In both death reports and overdose cases, ketamine was preponderant: 89.1% and 79%, respectively. No cases of overdose or death related to the use of ketamine as an antidepressant in a therapeutic setting were found; most of the deaths occurred in the circumstances of polydrug use and overdoses left no sequelae.

Conclusion: There is legitimate concern about the risks involving the use of ketamine and its analogues, especially in recreational settings. On the other hand, ketamine as medicine is considered safe and it is listed as an essential medicine by the World Health Organization. Although clinicians must remain vigilant, this should not deter appropriate prescription.

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Ketamine; drug overdose; toxicity; phencyclidine; dissociative anesthetics

Introduction

Ketamine is quickly taking its place as a therapeutic option in the management of treatment-resistant depression, yet the misuse of it continues to be a worldwide issue (1–8). Because of the limited duration of ketamine's antidepressant effect, it is necessary to re-dose it after a few weeks. Clinicians applying ketamine infusions either once or more often need to consider the addictive potential and the risk of inducing psychosis-like symptoms (2).

Non-medical use of ketamine was recognized in the United States when the Food and Drug Administration (FDA) expressed concerns about it in 1979. In Europe, it came to public attention in the 1990s, following the seizure of almost 100,000 ketamine tablets in the United Kingdom. They bore a logo usually found on ecstasy tablets, and some users suffering anxiety attacks were hospitalized after taking large doses of ketamine believing it to be ecstasy (9).

The first experiment with ketamine on human subjects was performed in 1964 on a sample of 20 volunteers from a prison population. It was the first investigation describing the multiple pharmacological effects of ketamine, including its anaesthetic analgesic, and antidepressant effects. That is when the term "dissociative anaesthetic was put forward to describe the mental state produced by ketamine, because it was observed that the subjects became somewhat disconnected from their environment under ketamine's influence (10,11). Outside the medical setting, ketamine and its analogues have been used for recreational and psychonautic (i.e. exploration of altered states of consciousness) purposes since the 1960s (12).

This article includes drugs from the same chemical group: arylcyclohexylamines. Phencyclidine or phenylcyclohexyl piperidine (PCP) is believed to be the first arylcyclohexylamine with recognized anaesthetic properties. Clinical studies on humans showed a tendency

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toward emergent delirium, which was often quite prolonged. It led to the discovery of ketamine, which has a shorter half-life, so the emergence phenomena are short lived and can be easily controlled. Several other drugs were designed based on PCP and ketamine. In this article, they are referred to as ketamine analogues (13–15).

Recreational users of ketamine are broadly divided into: (a) hospital and veterinary-adjacent staff (and their friends) who have access to the drug and are more likely to inject the liquid, resulting in primarily psychedelic effects, and (b) users primarily linked with the dance culture who take ketamine powder by the intranasal route, resulting in more stimulant effects (16).

The use of ketamine analogues, such as phencyclidine (aka PCP, angel dust), methoxetamine (MXE) and dizocilpine (MK-801) is also a point of concern. In Sweden, Bäckberg et al. (2015) described how the use of methoxylated PCP analogues (3-methoxy-phencyclidine or 3-MeO-PCP and 4-methoxy-phencyclidine or 4-MeO-PCP) was first noted in mid-2013. They have found that intoxications involving new psychoactive substances (NPS) and poly-substance use were common (17). Furthermore, Chong et al. (2017) described a ketamine analogue in the streets of Hong Kong: 2-Oxo-PCE (deschloro-N-ethyl-ketamine). In Hong Kong, ketamine was the second most commonly misused drug after heroin, in the period from 2007 to 2010 (18,19). There are suspicions around the substitution of ketamine for 2-Oxo-PCE in street supplies, possibly for evading detection (20).

Ketamine's use pattern has features in common with club drugs and cocaine misuse. Patterns of binge use are well described, as are the effects of acute intoxication (12,21–24). The most appealing aspects of ketamine for two-thirds of the users studied by Muetzelfeldt et al. (2008) were a "melting into the surrounding" feeling, visual hallucinations, out-of-body experiences and giggliness (25).

Similarly to phencyclidine, ketamine causes analgesia and amnesia without the cardiovascular and respiratory depression associated with common anaesthetics However, overdose, overly rapid infusion or combination with other drugs can cause respiratory depression, apnea, hypotension, bradycardia, myocardial infarction, seizure, stupor and coma (26). In a study using mice, Sarton et al (2001) observed that ketamine interacts with the mu-opioid receptor system, contributing significantly to ketamine-induced respiratory depression. Opioid and NMDA receptors and their endogenous ligands are found in large concentrations in areas of the central nervous system involved in respiratory control. Both receptor systems are important in the central formation of breathing activity and respiratory plasticity. The endogenous opioid system has a modulatory role in respiratory rhythmogenesis and the administration of exogenous opioids results in respiratory depression. NMDA receptors play a role in central CO_2 chemoreception and respiratory rhythmogenesis; they are also involved in the central processing of afferent input from the carotid bodies, and they play a role in the short-term potentiation of breathing (27).

Another study carried out in Hong Kong analyzed 233 records of ketamine use. The most common symptoms of ketamine misuse were impaired consciousness (45%), abdominal pain (21%), lower urinary tract symptoms (LUTS) (12%), and dizziness (12%). The most common abnormal physiological findings were high blood pressure (40%), followed by tachycardia (39%), abdominal tenderness (18%), and white powder in the nostrils (17%) (28). Additionally, repeated use of ketamine for recreational purposes affects prefrontal dopaminergic transmission. Repeated exposure to ketamine is associated with up-regulation of D_1 receptors in the dorsolateral prefrontal cortex. Thus, repeated use of ketamine might be associated with detrimental effects on brain neurotransmission (29).

In a review article on ketamine misuse, Bokor and Anderson (2014) reported that death from ketamine's acute direct toxicity is rare, but it can happen from drug interactions or from accidents (30). Vroegop et al. (2007) also observed that there are few reports of deaths caused exclusively by ketamine (31). It is noteworthy that poly-substance use is very common among ketamine and NPS users (17,32). For instance, in a study of 100 ketamine users, Dillon et al. (2003) noticed that ketamine appeared to be added to an already extensive drug use repertoire of a well-educated and informed sample of drug users in Sydney, Australia (33).

The aim of this systematic review is to outline the cases of overdoses and deaths related to the use of ketamine and/or its analogues as reported in the scientific literature, providing material to investigate if ketamine is safe in a therapeutic context, particularly in its use as an antidepressant. Furthermore, this review aims to inform those who prescribe ketamine for the treatment of medical conditions, as well as those working on drug education and/or harm reduction.

Method

Data collection for this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements (34).

Search strategy

Electronic searches were performed on the following databases: PubMed, EMBASE and CINAHL. Data collection was performed in July 2019, at the University of Groningen Library, The Netherlands.

The following search string was used in all searches: ["ketamine" OR "phencyclidine" OR "methoxetamine"] AND ["death" OR "mortality" OR "drug overdose"].

Inclusion and exclusion criteria

Articles describing cases of overdose and/or death associated with ketamine and/or its analogues were included.

The exclusion criteria were: (1) articles not available in English, Portuguese, Spanish, French or Dutch; (2) studies performed on non-human animals.

Data extraction

The studies included in this review were divided into two analysis axes: one axis comprised the articles describing cases where ketamine and/or its analogues were associated with death, and the other axis consisted of articles describing cases where these substances were associated with overdoses.

A data extraction form was developed and applied by one of the reviewers (TVC). This form focused on the following information: first author's name, publication year, number of cases described, demographics, location, ketamine analogue involved, and a brief description of the cases. Another author (ZMS) checked the extracted data. Discrepancies between the two reviewers regarding study eligibility were resolved through consensus.

Study selection

The search strategy yielded 3105 results. After the removal of duplicates, this number dropped to 1753. Their titles were screened and 298 articles were selected for full-text analysis, which resulted in the 34 articles included in this review. Figure 1 shows the PRISMA flowchart describing the selection and inclusion processes. Table 1 provides the classification of the excluded records after screening.

Results

From the sample of 34 articles, eighteen describe fatal cases and sixteen describe overdoses. Importantly, some cases of over-sedation (i.e. cases that were not connected to drug misuse) were included as overdose cases. Tables 2 and 3 give an overview of each article included in this review.

Ketamine analogues mentioned in the selected articles were: MK-801, 2-Oxo-PCE, 3-MeO-PCP, MXE and PCP. Poly-substance use was mentioned in 53% of the selected articles (19/34).

Most cases were males and the variety of ages was broad: from two to 65 years old.

From Asia, three articles were included (9% of the sample): two from Hong Kong describing overdoses cases and one from China portraying a fatality. The sample also contains fifteen European articles (44%) and sixteen North American publications (47%).

A total of 312 overdose cases were reported. Two publications from Hong Kong portray 188 overdose cases involving ketamine (8) and 56 overdose cases involving 2-Oxo-PCE (57), which constitutes a large sample size when compared to the other studies included in this review. Among all the overdose cases, ketamine was the predominant substance (246 cases = 79%), followed by 2-Oxo-PCE (56 cases = 18%), MXE (6 cases = 2%) and PCP (4 cases = 1%). Over-sedation of children was described in three publications (53,54,56), where three cases received five times the intended dose of ketamine, seven cases received ten times the intended dose and, remarkably, one case received 100 times the intended dose. In all cases, the over-sedation was closely monitored and it produced no sequelae. Another over-sedation case occurred with an elder patient: he received ten times the intended dose. After ketamine was administered, there were no signs of any problems until his waking up appeared to be unusually prolonged. Despite this, the patient did not demonstrate any systemic effects (58).

The development of tolerance was reported by Bonnet (2015) in a case where a nurse was self-injecting 50 mg of ketamine intramuscularly once a week to cope with her depression. Due to a gradually developing tolerance to the ketamine's antidepressant effect, she increased the dose and frequency of injections, reaching 2 g daily over the course of six months. Fourteen weeks after ketamine withdrawal, she presented with a normal condition without any detectable sequelae (52).

In the articles on deaths, 138 cases were reported in total, from which 87 came from one single publication (47). Ketamine was the preponderant drug in this group (123 cases = 89.1%), followed by MXE (11 cases = 8%), 3-MeO-PCP (2 cases = 1.5%), MK-801 (1 case = 0.7%) and 2-Oxo-PCE (1 case = 0.7%).

The only MK-801 case involved a man who bought it in an attempt to treat a self-diagnosed depression (35).

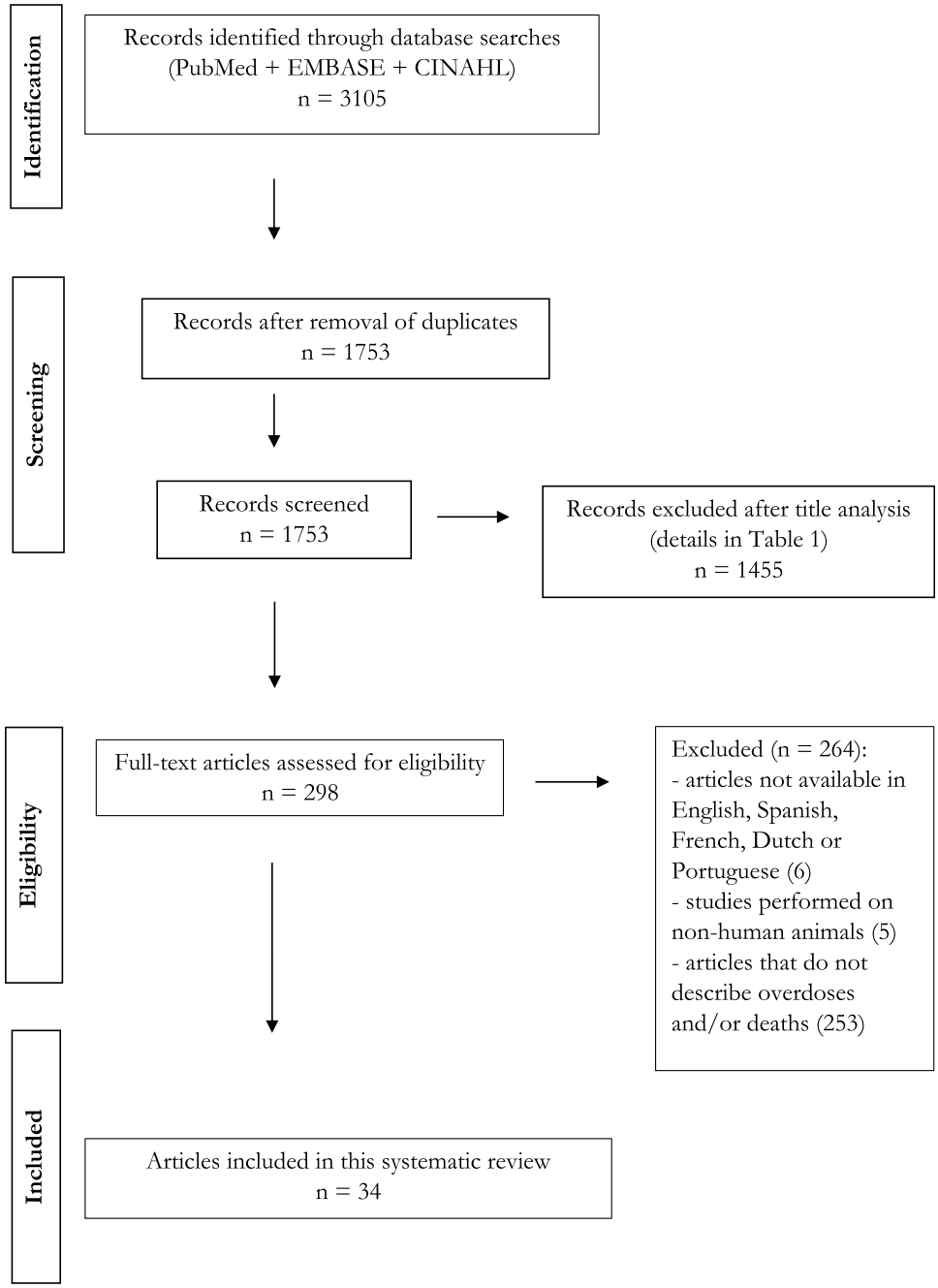

Figure 1. PRISMA flowchart.

Table 1. Classification of excluded records after screening (n = 1455).

Articles about the side effects associated (or not) with recreational use, misuse, chronic use, dependence on ketamine and/or its analogues	532
Studies performed on non-human animals	16
Reviews, letters, books	115
Articles about the therapeutic use of ketamine (i.e. treatment of depression, pain, alcohol dependence; sedation for medical procedures)	792

Table 2. Deaths related to the use of ketamine and its analogues.

Study	Number of cases	Location	Demographics	Ketamine analogue involved	Cause of death
Mozayani et al. (35)	1	United States	45-year-old male	MK-801	Acute toxicity related to the combined consumption of benzodiazepine, MK-801 and ethanol.
Adamowicz and Zuba (36)	1	Poland	29-year-old male	MXE	Acute toxicity related to MXE.
Breitmeier et al. (37)	1	Germany	28-year-old male	ketamine	Autoerotic accident. The gag and the drug-induced respiratory depression combined with cerebral edema caused inadequate oxygenation, resulting in central paralysis leading to fatal asphyxia.
Chiappini et al. (38)	8	United Kingdom	7 males +1 female Median age: 27 years old	MXE	7 died from drowning or from substance abuse. One died from ischemic heart disease.
Dinis-Oliveira et al. (39)	1	Portugal	29-year-old man	ketamine	Suicide by hanging. Under the influence of ketamine and alcohol.
EMCDDA* (9)	3	Ireland France	2 people One 19-year-old male	ketamine	Ketamine was not considered to be the cause of death in the Irish cases. Ecstasy and LSD were also found in his body.
Lalonde and Wallage (40)	2	Canada	26-year-old male 20-year-old male	ketamine	26-year-old male: ketamine intoxication. 20-year-old male: asthma. Ketamine was considered an incidental finding.
Mitchell-Mata et al. (41)	2	United States	21-year-old male 52-year-old male	3-MeO-PCP	Acute intoxication due to poly-drug consumption.
Wiergowski et al. (42)	1	Poland	31-year-old male	MXE	Multi-organ dysfunction syndrome caused by MXE and amphetamine use.
Theofel et al. (43)	1	Germany	52-year-old male	2-Oxo-PCE	The combination of 2-Oxo-PCE with venlafaxine.
Wikström et al. (44)	1	Sweden	26-year-old male	MXE	Acute intoxication with MXE, although the presence of 3 synthetic cannabinoids may have contributed to the death.
Tao et al. (45)	1	China	34-year-old female	ketamine	Chronic ketamine poisoning The court investigation revealed that she was poisoned by her husband over a period of 1 year in an act of homicide.
Licata et al. (46)	1	Italy	18-year-old male	ketamine	Massive pulmonary edema caused by ketamine overdose. It was a homicide caused by ketamine poisoning.
Gill and Stajíc (47)	87	United States	Non-hospital deaths (n = 15): 11 males +4 females Hospital deaths (n = 72): not mentioned	ketamine	Non-hospital deaths (n = 15): 12 due to acute multidrug intoxications, 2 due to physical injury and 1 due to sarcoidosis. Hospital deaths (n = 72): 54 acute traumatic deaths that had emergent surgery +18 burn and paediatric/obstetric surgical deaths.
Gaillard and Pépin (48)	1	France	Between 25 and 30-year-old female	ketamine	Acute intoxication caused by the combination of heroin, cocaine, cannabis, thiopental, ketamine and chloroform.
Moore et al. (49)	1	United States	32-year-old male	ketamine	Accidental ketamine and ethanol intoxication.
Peyton et al. (50)	2	United States	(1) 31-year-old female (2) 46-year-old male	ketamine	(1) Accidental ketamine intoxication. (2) Gunshot victim who was given ketamine during surgery.
Schifano et al. (51)	23	United Kingdom	19 males +4 females 19–49 years old	ketamine	In 4 cases: ketamine intoxication (3 accidental +1 suicide) In the remaining cases: 17 multidrug intoxications, 1 drowning and 1 stab wound to the chest.

*European Monitoring Center for Drugs and Drug Addiction.

An interesting case related to ketamine was an autoerotic accident involving a fatal combination of asphyxia by suffocation and intoxication with self-administered intravenous ketamine (37). Another, also interesting case from Portugal described a suicide by hanging under the influence of ketamine and alcohol (39). Besides that, two non-intentional and non-hospital cases were included, more specifically, two homicides. One involved a chronic ketamine poisoning of a woman by her husband (45); the other involved a teenager who was found dead in a car (46). The other fatal cases were mostly associated with regular recreational use of ketamine and/or its analogues in combination with other drugs.

Ketamine and/or its analogues were considered the exclusive cause of death in only nine cases (6.5%): one with MXE (36) and the eight others with ketamine (40,45,46,50,51). Acute intoxication caused by poly-

Table 3. Overdoses related to the use of ketamine and its analogues.

Study	Number of cases	Demographics	Location	Ketamine analogue involved	Brief description
Bobo and Miller, 2002	1	20-year-old male	United States	ketamine	Accidental lorazepam and ketamine overdose.
Nogué et al., 2015	3	24-year-old male 20-year-old female 23-year-old female	Spain	MXE and ketamine	The 24-year-old male was referred after an episode of seizures associated with brain injury. He had used ketamine, cocaine and alcohol before the episode. The females claimed that they had been sexually assaulted under the influence of a chemical submission. Laboratory analysis confirmed the presence of MXE in their samples.
Bonnet (52)	1	Anaestheticnurse	Germany	ketamine	Use of ketamine to self-treat depression. Due to tolerance, the dose increased from 50 mg once a week to 2 g daily.
Bowman et al. (53)	1	2-year-old female	United States	ketamine	For sedation, 23 mg of ketamine was ordered. By mistake, 230 mg was administered.
Capapé et al. (54)	1	3-year-old male	Spain	ketamine	For sedation, 45 mg of ketamine was ordered. By mistake, 450 mg was administered.
Coger and Donnelly (55)	1	49-year-old male	United States	ketamine	The administration of 5 to 30 mg per hour was permitted for pain management. By mistake, the patient received a dose sufficient to induce anesthesia.
Green et al. (56)	9	children	United States	ketamine	Three patients received 5 times the intended dose; 5 patients received 10 times the intended dose; 1 patient received 100 times the intended dose.
Marshman et al., 1976	3	20-year-old male 18-year-old female 26-year-old male	Canada	PCP	Multiple drug abuse in all cases.
Maskell et al., 2016	1	29-year-old male	United States	MXE	Use of MXE for its analgesic effects to treat chronic foot pain from a surgery one year prior. He had ingested up to 10 mg every 4 hours for 5 days before being found by the police lying in front of oncoming traffic.
Ni et al., 2018	22	People of all ages	United States	ketamine	20 out of 22 used ketamine with other drugs.
Stockard et al., 1976	1	25-year-old male	United States	PCP	The electroencephalographic findings were similar to that of deep anesthesia from ketamine.
Tang et al. (57)	56	36 males from 24 to 52 years old 20 females	Hong Kong	2-Oxo-PCE	In 31 cases, other drugs of abuse were detected. In 25 cases, 2-Oxo-PCE was used alone. Three patients required intensive care.
Warner and Smischney (58)	1	65-year-old male	United States	ketamine	By mistake, the patient received 950 mg instead of the intended 95 mg.
Weiner et al. (59)	20	11 males 9 females	United States	ketamine	Eleven patients stated that the injected dose was between 100 and 200 mg. Two patients admitted the concomitant use of LSD and methamphetamine.
Wood et al., 2012	3	28–42 years old	England	MXE	They presented at the emergency department on unrelated occasions. Other drugs were detected in their blood.
Yiu-Cheung (8)	188	Predominantly male Majority were between 10 and 39 years old	Hong Kong	ketamine	Ninety cases presented with neurological features, such as confusion and drowsiness. Sixty cases had lower urinary tract symptoms consistent with ketamine cystitis.

substance misuse was the cause of death in one third of the cases (9,35,38,41–49,51). In the other two thirds, ketamine and/or its analogues were present, but the causes of death were diverse, for example: asphyxia (37), heart disease (38), suicide by hanging (39), asthma (40), trauma that had emergent surgery (47), sarcoidosis (47), and drowning (51). In two cases the cause of death was not mentioned in the article (9).

Discussion

This systematic review gives an interesting insight into the ever-present doubts regarding the safety of ketamine and its analogues. A total of 138 cases of death were found in the literature, and most of them occurred in the circumstances of polydrug use. Overdose was described in 312 cases.

The description of the overdose and death cases provided by this review intends to provide relevant information to health care professionals and to people working on drug education and harm reduction. An earlier article from the authors discusses the interest of ketamine users in having access to scientifically assessed information about the drugs they use or are willing to use, in order to avoid the deleterious effects that these drugs can cause. Thus, drug education and harm

reduction are essential in keeping drug users up to date, which may reduce the burden of drug-related problems in the health care system and may provide a better drug experience to the users (60).

Because of its potential to cause drug dependence, the use of ketamine as an antidepressant can be avoided by some prescribers, hence the importance of discussing how risky and dangerous ketamine can actually be. Scientific data suggest that its use to manage depressive symptoms requires close medical monitoring, which can be done by applying validated questionnaires (such as "The drug abuse screening test" (61) and the "Systematic assessment for treatment emergent events" (SAFTEE) (62)), monitoring the vital signs and performing laboratory assessments.

This review found 73 cases of death in the clinical setting, however, in none of these cases, intoxication by ketamine or its analogues was considered the causa mortis. The 72 cases described by Gill and Stajíc (2000) and the case described by Peyton et al. (1988) concern deaths during surgery, where ketamine was used as an anaesthetic(47,50). The overdose cases in the clinical setting were caused by mistakes in the administration of the drug and left no sequelae (53–56,58). No cases of overdose or death related to the use of ketamine as an antidepressant in a therapeutic setting were found.

An excessive and dangerous dose, i.e. an overdose, seems to be effectively managed with the administration of benzodiazepines and time (53,54,56). However, considering the popularity in mixing drugs for recreational purposes, it is essential to keep in mind that a patient experiencing a ketamine overdose might have used other drugs concomitantly. More than half of the articles (53%) included in this study mentioned the simultaneous consumption of several drugs (also known as poly-substance use, polydrug use, or multidrug use), which increases the risks for severe and unpredicted consequences. This investigation corroborates the concerns around these risks. Ketamine and its analogues were rarely used alone and the danger of having accidents while under the influence of drugs is ever-present (e.g. the autoerotic accident described by Breitmeier et al., 2012) (37).

From 2005 to 2013, 317 new illegal psychoactive products were identified in Europe (63). Some NPS, such as MXE, are marketed as a "bladder safe" derivative of ketamine (59). Phencyclidine was released for veterinary use under the trade name Sernylan. It appeared illicitly in 1967, marketed as the PeaCe Pill in San Francisco, United States (14). Since then and to this day, several ketamine analogues are emerging from the underground culture.

Luethi and Liechti (2020) state that, because of their novelty, designer drugs may remain undetected by routine drug screening, thus hampering evaluations of adverse events. Their analysis of intoxication reports corroborates with the findings of this study: several designer drugs are used concurrently, posing a high risk for severe adverse events or even death (64). Therefore, this study included the information not only about phencyclidine and ketamine, but also the data concerning several drugs that are being designed based on phencyclidine and ketamine molecules, hence the inclusion of designed arylcyclohexylamines (the analogues).

During data collection, a significant number of studies carried out in Hong Kong were found on ketamine misuse and its deleterious effects (65–67). The misuse of ketamine has been highly popular among Hong Kong teenagers since 2005. It is also the fourth most common poison encountered in the 2010 data from the Hong Kong Poison Information Center (8). In other places in Asia, it is remarkable how many studies have been conducted on ketamine and its harmful effects on the lower urinary tract, causing ketamine-related cystitis and many other LUTS (7,68–71). In China, ketamine is an increasingly popular drug of misuse and, consequently, the number of dependence cases is rising. To improve the management of ketamine dependence, Fan et al. (2015) are developing a checklist of short and long-term symptoms associated with ketamine dependence, alongside a classification of its psychological effects (72). Moreover, a Spanish team of researchers elaborated and validated the Severity of Dependence Scale in a sample of 264 recreational ketamine users (73).

A limitation of this study is given by the definition of "deaths related to the use of ketamine and its analogues." The fact that a drug was detected postmortem does not necessarily imply that it contributed directly to the death. The studies included in this review have several methodological limitations. Most of them have a cross-sectional nature, which limits the inference of causal associations. Moreover, since they are not experimental studies, it is not possible to measure the dose of ketamine or analogue consumed, nor the pharmacological interaction among different drugs. Another limitation of this study is the absence of information other than academic literature. Data from poison control centers and media (i.e. data available in the public realm) were not included because it would require more human resources, funding and time.

There is legitimate concern about the risks involving the use of ketamine and its analogues. Their dissociative effect increases vulnerability and recklessness, leaving its users more exposed to accidents and/

or misguided decisions. Their misuse and chronic use can produce an assortment of symptoms: neurotoxicity, cognitive impairment, urinary tract damage, dependence and withdrawal issues. On the other hand, ketamine as a prescribed medicine is considered safe and it is listed as an essential medicine by the World Health Organization. Although prescribers must remain vigilant, this should not deter appropriate prescriptions. Finally, prevention and harm minimization campaigns are needed to alert people to the potential damage that can be caused by the acute and chronic use of ketamine and its analogues.

Disclosure statement

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