

Ketamine abuse: Another side of the miracle drug (A case report)

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Abstract

Ketamine is a “ dissociative anaesthetic “ with fast analgesic and amnesic properties that has been used since more than 40 years. Today, ketamine abuse has become a public health concern. We report the case of a 23-year-old patient who came to the Casablanca Addictology Centre asking for help with ketamine abuse. At the interview the patient presented depressive symptoms and had already made 3 suicide attempts, the last one dating from two months ago. Mr J. started his consumption of psychoactive substances during adolescence (age 14) by experimentation, the first substance was tobacco followed by crack, alcohol and ketamine. The ketamine dependency started one year ago, with 2 grams of ketamine snorted per occasion (twice a week). The reported psychoactive effects of ketamine ranged from dissociation and depersonalisation to psychotic experiences. The patient has never made a withdrawal attempt. Given the increasing therapeutic importance of ketamine, our aim was to highlight the other side of the problem, the significant risk of ketamine abuse. Thus, in this article we tried to review the history of ketamine, its growing role as a “dance drug”, as well as the specifics of the management of ketamine misuse. In conclusion, the clinicians must stay vigilant, however this should not be a deterrent to appropriate prescribing.

Keywords: Ketamine, abuse, addiction.

Abbreviations : mPFC: Cortex prefrontal median; DSM-5 : manuel-diagnostique-et-statistique ; NMDA: N-méthyl-D-aspartate; NAc : Noyau accumbens; SNC: Système Nerveux Central

Introduction

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist, a mu and sigma opioid receptor agonist and has a long history of use as an anaesthetic agent in humans and in veterinary Medicine [1]. New findings about ketamine's antidepressant and antisuicidal characteristics give hopes for an effective treatment for major depressive disorder [2].

However due to its reinforcing and motivating properties, ketamine has [3] become a recreational drug in the context of raves and its non medical use has been increasing worldwide over the last decades [4].

The first cases of ketamine abuse were reported in France in 1992, leading to special surveillance by the health authorities and its inclusion in the list of narcotics in 1997 [5]. Ketamine has subsequently been known as a drug of abuse ("Special K") because of its disassociative effects [6]. Those characteristics

of ketamine contribute greatly to ketamine abuse [7]. Recreational doses of ketamine are about 15% to 20% lower than its anaesthetic dose [8].

Today, ketamine abuse has become a public health concern [9]. In response to the increasing therapeutic interest shown for ketamine, our aim was to address the other side of the problem, which is the high risk of ketamine abuse. Hence, in this article we attempted to review the history of ketamine, its growing role as a "dance drug", as well as the specifics of the management of ketamine misuse.

Observation

We report the case of a young single man, Mr J. H., aged 23 years old. He had a high school degree and was living alone. He was working in a call centre and at night as a club DJ. The patient came to the addictology centre asking for help with ketamine addiction. As for his psychiatric history, he had been

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treated since the age of 15 by a number of child and adolescent psychiatrists for addiction with attempted suicides and had been put on various medications but with very irregular follow-up and had no other medical or surgical history. For the addiction history, Mr J. started his consumption of psychoactive substances during adolescence (age 14) by experimentation, the first substance was tobacco followed by crack, alcohol and ketamine. The ketamine dependency started one year ago, with 2 grams of ketamine snorted per occasion (twice a week).

The patient described his experience with ketamine as unique. He felt light, euphoric, had pleasant visual hallucinations of animals and also had the impression that his body was separated and that he was floating in the sky, other depersonalizing sensations. Although these effects persisted for about 45 minutes, he had the impression that time had stopped around him and he was in this state for hours. Over time, he had decreased his use of other drugs and ketamine became the substance of abuse. He also developed a significant tolerance to ketamine. On withdrawal, he described distinctive symptoms, which were attenuated by alcohol use, with no significant physical withdrawal symptoms. It should be mentioned that the patient had never consulted for detoxification and had not yet made any withdrawal intentions.

At the first visit, the patient was slowed down, presented a depressive state, a high level of self-blame, insomnia and had suicidal intentions (three suicide attempts, the last of which was two months ago by medication). He had a severe addiction according to DSM5 criteria and was in the pre-contemplation stage. He received symptomatic treatment as well as antidepressant treatment (fluoxetine 20 mg/d) but did not return to the consultation for follow-up.

Discussion

Prevalence of Ketamine Abuse

Ketamine abuse has been increasing quickly over the last 20 years [10]. A US survey estimated that there was an increase in self-reported non-medical ketamine use compared to the previous year from 2006 to 2014 ($B = 0.21$; $P = 0.030$) and an increase from 2015 to 2019 ($B = 0.29$; $P = 0.036$), with a peak of 0.9% in late 2019[11]. This strong evidence of ketamine's addictive potential was confirmed by another Australian study including 100 users of recreational ketamine which found that about one in five participants (22%) reported having physical tolerance to ketamine[12]. In Asia, the number of ketamine users almost increased four times in Malaysia between 2006 and 2012 [13]. Ketamine is the second and third most abused drug in Hong Kong and mainland China and Taiwan respectively [14]. It is most commonly consumed by young people [15], gay nightclubbers [16] and poly-drug users [17]. In the case of our patient, the first experience with ketamine was not a result of a medical prescription. MR JH is a young man, who had

multiple substance use and who worked in a night club. All these factors may contribute to the initiation of ketamine use.

Pharmacological Properties of Ketamine

Ketamine has a chemical structure composed of two pure optical isomers, the S- and R-ketamine, and each racemate consists of the two isomers in equal parts. The (S) enantiomer has higher affinity for NMDA [18, p. TUY] and a 4-fold higher anaesthetic potency than the R(-) isomer [19]. The predominant mode of administration of ketamine for recreational use is sniffing, and the intravenous injection is relatively rare [20]. Hashimoto et al 2020 evaluated another physiological indicator of drug reward, the release of dopamine, by measuring the regional uptake of 18F-fallypride, a dopamine receptor ligand that can be displaced by promoting dopamine release. (R)-ketamine preferentially reduced 18F-fallypride uptake in the NAc, while (S)-ketamine seemed to further stimulate dopamine release in the prefrontal cortex and other regions. (S) ketamine is apparently responsible for the reward properties of ketamine [21]. A further study identified a selective activation of mu and kappa opioid receptors by (S)-ketamine in the medial prefrontal cortex (mPFC). These results suggest that the abuse risk of ketamine in humans is principally attributed to the pharmacological effects of its enantiomer (S) [9]. In 2019, the FDA approved the enantiomer S-ketamine, in an intranasal spray (Spravato), for the adjunctive treatment of treatment-resistant depression (TRBD), and in 2020 for the treatment of major depressive disorder with acute suicidal ideation or behavior [22]. In addition, intravenous ketamine is also used off-label as an adjunctive treatment for resistant bipolar depression, although the safety and efficacy of this treatment still await more studies [23].

Although the abuse potential of (R,S)-ketamine is well established in animals, there is limited clinical evidence that both single and repeated administrations of ketamine in controlled clinical conditions have not led to abuse, dependence, misuse and/or gateway behavior in patients with TRD [18].

Symptoms of ketamine abuse

Ketamine's positive reinforcing properties include anesthesia, euphoric and dissociative effects. A low dose is associated with a feeling of relaxation, called "K-land", while a higher dose induces a dream like state, called "K-hole" [24]. Reports of "out-of-body" experiences have been consistently associated with recreational use and abuse of ketamine [25]. These feelings disappear about 2 hours after acute ketamine use [8]. The K-hole experience is known to vary between users [19]. In this case report, snorting was the most mode of administration of ketamine. The patient felt light, euphoric, had pleasant visual hallucinations and depersonalizing sensations. The most common symptoms of ketamine withdrawal observed are discomfort, fatigue, reduced appetite and energy. As well as sleepiness, craving, panic attacks and dysphoria [3]. And finally, because of the CNS-modulating activity of ketamine, it

should be used with caution with other drugs that affect mood and perception, including alcohol, opioids, benzodiazepines and cannabis [19].

Many neurological side effects of ketamine abuse are dose-dependent, although most of them are self-limiting. These effects include hypersalivation, hyperreflexia and transient clonus [26]. Ketamine may also cause vestibular type symptoms including dizziness, nausea and vomiting. The cardiopulmonary toxicity of ketamine is rare, being limited to effects caused by transient sympathetic activation such as tachycardia, hypertension and palpitations. [27]. More recently, cases of cystitis and other lower urinary tract symptoms (e.g. detrusor overactivity) have also been reported in chronic ketamine users [28].

Both clinical and animal studies confirm the liver damage caused by chronic ketamine use. Bile duct dilatation, microscopic bile duct damage and even significant liver fibrosis have been observed in ketamine users [29]. These adverse effects are potentially reversible with abstinence [30].

It is interesting to note that in the recent systematic review of the literature by Walsh ANDal 2021, there were no reports of ketamine use/abuse after ketamine treatment, neither any evidence of transition from medical to non-medical use of ketamine [31].

Treatment of ketamine abuse

There is still no specific guideline in the literature for the management of Ketamine dependency. A recent study, based on the primary pharmacological action of ketamine, reported a significant decrease in the frequency and daily dose of ketamine among a chronic ketamine user who received an administration of lamotrigine, a glutamate release inhibitor [32]. Like other substance use disorders, behavioural and cognitive therapies have also been the main approach to managing compulsive use behaviours in patients with ketamine dependence [8].

Conclusion

Ketamine has many interesting therapeutic advantages. However, there is a legitimate concern about the risks associated with the use of ketamine and its analogues, particularly in recreational situations. Thus, the use in patients with substance use disorders should be subject to higher and more stringent criteria. However, although clinicians should remain vigilant, this should not discourage appropriate prescribing.

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