Medical Sciences

Relapse on ketamine followed by severe and prolonged withdrawal: A cautionary case and review of potential medical therapies

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Ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist used medically as a dissociative anesthetic. It has been used recreationally since the 1970s. In recent years, ketamine has been investigated in the treatment of depression and chronic pain. Given ketamine's addictive potential, increasing medical use poses the risk of misuse or addictive use following medical exposure. This risk may be higher in patients with co-occurring substance use disorders (SUD). We present the case of a patient with opioid use disorder well-controlled on buprenorphine who was exposed to ketamine in the emergency department (ED), then relapsed by misusing ketamine. He procured it from the darknet to "self-medicate his depression." After using heavily for 15 days, he experienced debilitating withdrawal syndrome requiring intensive care unit admission. Ketamine use should be in the differential of any young patient who presents to the ED with agitation and visual hallucinations or nystagmus. Moreover, the benefits of therapeutic ketamine use should be weighed carefully against the risk of misuse or addictive use. In cases where ketamine use is absolutely necessary for high-risk patients, we recommend that dosing be limited to the sub-dissociative range (0.2-0.5 mg/kg). We also recommend the use of a slow infusion rather than bolus. For patients with ketamine withdrawal, benzodiazepines and/or anti-glutamatergic anticonvulsants may be helpful to alleviate symptoms.

depression | ketamine | opioid use disorder

Introduction

Ketamine is an arylcyclohexylamine and was developed in 1962. It functions primarily as a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor [1]. Furthermore, NMDA-antagonism leads to increased release of glutamate, which can then activate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Additional postulated mechanisms of action include inhibition of L-type voltage-dependent calcium channels, monoamine reuptake inhibition and weak opioid agonism. Ketamine is a dissociative anesthetic. This term refers to the disconnect that subjects feel from their environment [2]. It was developed as a shorter-acting analog of phenicyclidine (PCP) and remains in use today for the induction and maintenance of anesthesia. It has an elimination half-life of 2-3 hours, but a distribution half like of 10-15 minutes [1]. It is particularly useful because it has minimal impact on the cardiovascular or pulmonary systems [3]. In recent years, it has been investigated as a rapid-acting antidepressant, analgesic, and for the treatment of opioid use disorder (OUD) [4-6].

American soldiers in the Vietnam War were given ketamine anesthesia because of its wide therapeutic range [2]. Subsequently, in the 1970s, recreational use of ketamine emerged. This led to ketamine being made a schedule III drug in 1999 [3]. In the United States, the prevalence of ketamine use among 12th graders was 1.2% in 2016, which has decreased from 1.7% in 2012 [7]. In 2015, there were a total of 1,568 reports of ketamine being seized, which is much less than the 4,751 seizures of PCP [8]. Conversely, in Hong Kong, ketamine is the most prevalent illicit drug and constitutes 85% of drug use in persons aged 21 or below [9]. Long-term use can cause pronounced and persistent neuropsychiatric symptoms including schizophrenia-like symptoms, cognitive impairment, worsening depression, ulcerative cystitis, and various lower urinary tract pathologies [1].

Deaths from ketamine use are likely to involve trauma due to the users' decreased awareness of their environment or co-ingestion of other drugs or toxins [10]. In a case series of 233 ketamine users presenting to an emergency department (ED) in Hong Kong, impaired consciousness, abdominal pain, lower urinary tract symptoms and dizziness were the most common complaints [9]. The most common physical findings were hypertension, tachycardia, abdominal tenderness and hyperthermia. Only five patients required intensive care unit (ICU) management and all of them had co-ingested other drugs. We present a case report of a patient with OUD who after exposure to ketamine in a medical setting, initially sought to "treat his depression" with ketamine, but proceeded to use it heavily for 15 days leading to a debilitating withdrawal syndrome requiring ICU admission.

Case Presentation

A 34-year-old white male with a past medical history of ADHD, bipolar disorder, type II, essential tremor and OUD on maintenance therapy with buprenorphine had been stable with regular follow-up in our dual diagnosis clinic for two years. Over those two years, he attested to abstinence from all substances other than the ones prescribed. This was corroborated by random urine drug screening (UDS) performed in our clinic and by using a prescription drug-monitoring database. The patient's medications are listed in table 1.

After a minor work-related injury, the patient developed an abscess on his arm and presented to our ED. Because of the patient's history of OUD on buprenorphine, the emergency medicine physician decided to use ketamine for analgesia rather than an opioid. The patient received an incision and drainage and had iodoform packing placed. Medications administered are listed in table 1. The abscess healed without any complications.

On a subsequent clinic visit three months later, he reported his baseline depression significantly improved. The patient has a doctoral degree in neuroscience and had read extensively about ketamine therapy for refractory depression. One month later, he returned and reported "terrible depression" and requested treatment with ketamine. He was informed that our clinic does not offer that service and was also made aware of the addictive potential of ketamine. Shortly afterwards, he procured ketamine

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Table 1: Medications

Generic Name	Dosage	Route	Frequency	Indication
Home Medications				
Buprenorphine	8 mg	s.l.	b.i.d.	Opioid dependence
Buspirone	15 mg	p.o.	b.i.d. p.r.n	Anxiety
Escitalopram	30 mg	p.o.	Daily	Bipolar II
Guanfacine	1 mg	p.o.	q.h.s. p.r.n.	ADHD
Propranolol S.R.	60 mg	p.o.	Daily	Essential tremor/Migraine prophylaxis
Emergency Department Visit #1				
Ketamine	176 mg (2 mg/kg)	i.v.	Once	Procedural sedation
Ondansetron	4 mg	i.v.	Once	Nausea
Ketamine	200 mg	i.v.	Once	Continued procedural sedation
Illicit Ketamine Use				
Ketamine, purity unknown	~1000 mg/day	i.m.	In divided doses every 2-3 hours	"self-medication"
Emergency Department Visit #2				
Divalproex sodium	500 mg	p.o.	Once	Myoclonus/ketamine withdrawal
Divalproex sodium	250 mg	p.o.	b.i.d.	Myoclonus/ketamine withdrawal
Emergency Department Visit #3				
Lorazepam	2 mg	i.v.	Twice	Agitation/ketamine withdrawal
Diphenhydramine	50 mg	i.v.	Once	Recommended by poison control in case abnormal movements were dystonic reaction
Normal saline	1 liter	i.v.	Once	Prevent rhabdomyolysis in agitated patient
Intensive Care Unit				
Dexmedetomidine	Variable	i.v. infusion	Continuous	Agitation/ketamine withdrawal
Olanzapine	2.5 mg	p.o.	q.i.d. p.r.n.	Hallucinations
Discharge Medications				
Chlordiazepoxide	Variable	p.o.	Variable	Ketamine withdrawal
Olanzapine	2.5 mg	p.o.	q.i.d. p.r.n.	Hallucinations

himself from the darknet. He reported that after paying with a digital currency, Bitcoin, the ketamine arrived at his home within six days from the European Union.

For a period of 12 days, he used an average of 1000 mg/day divided in 100-150 mg aliquots intramuscularly (IM) every 2-3 hours. He presented himself again to the ED, now requesting detoxification assistance. He reported that every time he tried to stop using ketamine, within an hour he developed marked worsening of his essential tremor, myoclonic jerking and an unsteady gait. He also complained of insomnia. Because these symptoms improved if he re-dosed ketamine, he was unable to discontinue use.

When examined, his vitals were stable, but he was noted to have nystagmus, piloerection, evidence of IM injecting on his upper extremities, and multiple ecchymoses on his lower extremities. A neurological exam was significant for hyperreflexia, intention tremor, dysmetria and gait ataxia. A mental status exam was significant for anxiety, pressured speech, and responding to both visual and auditory internal stimuli with disjointed and disorganized speech. Labs including complete blood count, comprehensive metabolic panel, thyroid studies, salicylates, acetaminophen, ethanol and UDS were within normal limits. An MRI brain with and without gadolinium and electrocardiogram were both normal. He was observed in the ED overnight with consultation from psychiatry.

The next morning, the patient was less anxious with more organized thought process and no hallucinations and with improved myoclonus, but gait was still impaired. His vital signs continued to be stable. He was not found to be holdable on a legal psychiatric hold and admission for further medical detoxification was not found to be indicated at that time. He was given a single dose of divalproex sodium 500 mg and on discharge was continued on 250 mg p.o. b.i.d. to aid with resolution of anxiety and for myoclonus. He was referred for inpatient rehabilitation. Instead, he opted for an intensive outpatient program, which was supposed to begin the following day. However, before presenting for treatment, he began using ketamine again at similar dosages. After another three days of use, he called emergency medical services because of fear of seizures, hallucinations, and "incredible shakiness and myoclonic jerking" which worsened if he stopped administering ketamine. He was brought to an outside ED.

Again, vitals were stable, but he was noted to be pale and diaphoretic with dry mucous membranes, and also to be extremely agitated and anxious. He was experiencing auditory, visual and tactile hallucinations. In the ED, he received a total of 4 mg of lorazepam, 50 mg of diphenhydramine IV and one liter of normal saline. After these failed to bring about significant improvement, he was transferred to the ICU and started on a dexmedetomidine infusion. Again, labs were all within normal limits and the UDS was negative.

In the ICU, he remained agitated and tremulous with no decrease in the hallucinations. As a result, he was started on olanzapine 2.5 mg p.o. q.i.d. as needed. His hallucinations and agitation improved and he was transferred to the progressive care unit and discharged on day seven. Upon discharge, his tremors and ataxia were still debilitating, but improved to a degree that he no longer required a walker. He was discharged with a chlordiazepoxide taper and reports this controlled his symptoms better than divalproex. Arrangements were made to follow-up at an evening treatment program and he complied. He completed this treatment successfully, but it took several months for his tremors and gait to return to baseline. At this writing, eight months later, the patient continues to have intermittent myoclonic jerks. He gave informed consent in the clinic for the case report to be published.

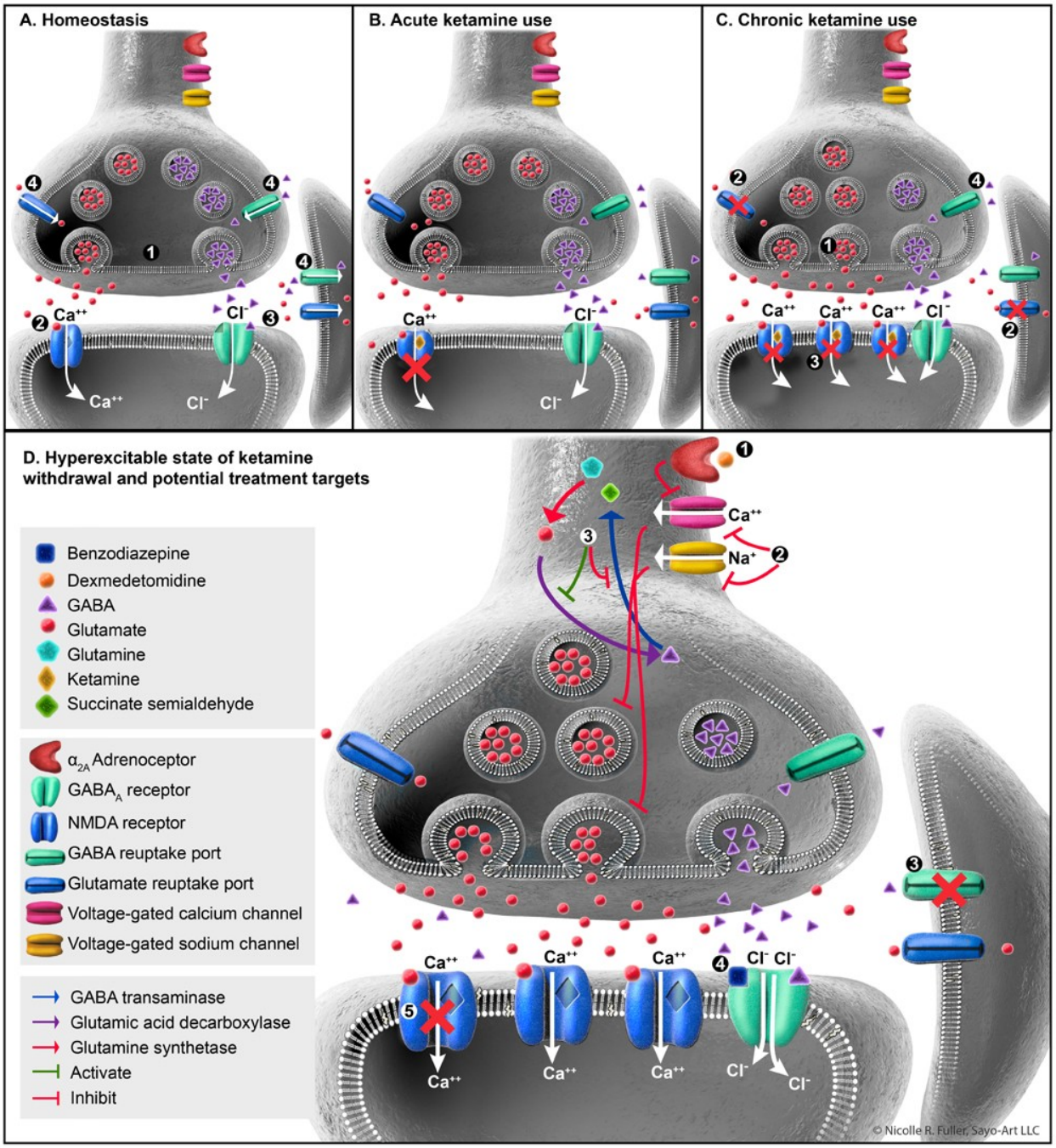

Figure 1: Synapse showing hyperexcitability in ketamine withdrawal potential treatment options. A) Synapse in homeostasis with a balance of excitatory and inhibitory signaling: 1) Vesicles of glutamate and γ-aminobutyric acid (GABA) are released into synaptic cleft [17]. They bind their corresponding receptors – the NMDA receptor for glutamate and the $GABA_A$ receptor for GABA. Other receptors for each ligand exist but are beyond the scope of this article. 2) Glutamate binds NMDA receptor causing its ion channel to open and an influx of positively charged calcium. 3) GABA binds the $GABA_A$ receptor and there is an influx of negatively charged chloride ions. 4) After dissociating from their binding sites, glutamate and GABA can be taken up again by ports on the presynaptic terminal or by astrocytes surrounding the synapse. B) Ketamine binds the NMDA receptor within the ion channel preventing flow of cations through the channel and preventing neuronal activation required for awake state [18]. C) With continued ketamine use, the glutamatergic system tries to compensate by three mechanisms: 1) Increased glutamine release from presynaptic terminal 2) Decreased reuptake from synaptic cleft by the ports within the presynaptic membrane and surrounding glial cells 3) Increased number of NMDA receptors [19]. D) When ketamine use is discontinued, the compensatory changes lead to hyperexcitability as there is now an imbalance between excitatory and inhibitory signaling. Drugs that have potential to correct this imbalance and their mechanisms of action are shown: 1) Dexmedetomidine – binds α_{2A} adrenoceptor on presynaptic axon leading to decreased voltage-gated calcium entry which leads to inhibition of glutamate release into synaptic cleft [20] 2) Lamotrigine – acts presynaptically to inhibit voltage-gated sodium and calcium channels which leads to decreased glutamate release into the synaptic cleft [21] 3) Valproic acid – increases GABA inhibitory effect by three different mechanisms – i) Activation of glutamic acid decarboxylase (catalyzes glutamate to GABA) ii) Inhibition of GABA transaminases (catalyze degradation of GABA to succinate semialdehyde) iii) Decreased uptake of GABA into astrocytes from the synaptic cleft 4) Benzodiazepines – positive allosteric modulators of $GABA_A$ receptor which causes increased chloride influx, hyperpolarizing the membrane potential and making postsynaptic neuronal activation less likely 5) Acamprosate – inhibits NMDA receptor mediated calcium influx, but the exact mechanism is unknown [22]. Using any of the above medications for treatment of ketamine withdrawal is not an FDA approved use.

Discussion

Ketamine intoxication should be suspected in patients presenting to the ED with symptoms of agitation, tachycardia and either visual hallucinations or nystagmus [11]. Routine UDS will not detect ketamine. Since ketamine's distribution half-life is short, symptoms not improving within two hours should raise suspicion of co-ingestion or an alternate disease process. The differential diagnosis for drug- or toxin-induced hallucinations should include LSD, hallucinogenic mushrooms, PCP, cocaine, amphetamines, anticholinergic drugs and plants such as morning glory, jimson weed and nutmeg.

In a case series of 30 daily ketamine users, 40% reported withdrawal symptoms characterized by anxiety, tremors, sweating and palpitations in addition to psychological complaints such as anxiety, craving, depression and insomnia [12]. The case we present is unique in that the withdrawal symptoms were prolonged and severe enough to require ICU admission. There is scant literature on the management of ketamine withdrawal. Supportive care, including intravenous fluids, should be provided. Benzodiazepines can be used to relieve anxiety and agitation, and if benzodiazepines are insufficient, a high-potency first-generation antipsychotic or second-generation antipsychotic may be tried [13]. Given that ketamine is an NMDA receptor antagonist, it is plausible that discontinuation could result in a glutamate rebound, leading to hyperexcitation and agitation. Indeed, lamotrigine has been shown to decrease the neuropsychiatric effects of ketamine [14]. A review of potential treatment options for hyperglutamatergic state is presented in figure 1. Additionally, several case reports have shown naltrexone to be useful in reducing ketamine cravings, potentially due to cross-sensitivity to mu-opioid receptors, but this would have been contraindicated in our patient on buprenorphine [15, 16].

It has been suggested that ketamine may be useful in the management of acute pain in patients with OUD [23]. In some cases, physicians have actually preferred it over opioids because of lower perceived risk of inducing relapse. However, as this case illustrates, ketamine also has addictive potential and may induce relapse in patients with SUD. Thus, if therapeutic use is absolutely necessary, we suggest keeping the dose in the sub-dissociative range, 0.2-0.5 mg/kg, and using a slow infusion rather than bolus to minimize euphoria and avoid triggering a relapse. Finally, as more patients with SUD turn to the darknet to procure their drugs, physicians should also be aware of these markets. It is prudent to emphasize, as found by a recent Dutch study, that these drugs are just as likely to be adulterated as those obtained on the street [24].

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