General Scholarly Article

Ketamine and its Regulatory Implications: A Review

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ABSTRACT:

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for use as a clinical and veterinary anesthetic since 1970. Although esketamine, a specific molecular form of ketamine, is FDA-approved for the management of treatment-resistant depression, regular ketamine is often used off-label at subanesthetic doses to treat depression as well as other psychiatric disorders and pain. Despite the lower doses of ketamine used for analgesia and depression, ketamine can cause dissociative, psychomimetic, and hemodynamic symptoms that require careful monitoring during and after administration. Over the past several years, rising public interest in ketamine has led to a "wild west" of so-called ketamine clinics, which offer off-label ketamine treatment, sometimes through compounding pharmacies, for a variety of conditions. These clinics are largely unregulated, representing a possible ongoing threat to the safety of patients which may merit action among state medical regulators. Regulations may be helpful for all of the stakeholders in the off-label ketamine marketplace, including distributors, compounding pharmacies, clinics, and providers themselves. In this article, the pharmacology of ketamine and evidence supporting off-label use are reviewed, along with suggestions for regulating the burgeoning ketamine clinic landscape.

Introduction

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for human and veterinary use as a clinical anesthetic since 1970. Ketamine is a derivative of phencyclidine (PCP) and was developed with the goal of reducing the hallucinogenic side effects, prolonged anesthesia recovery window, and abuse potential associated with the parent drug.[1] Although ketamine can still cause hallucinogenic or other psychotic symptoms, especially at high doses, it is nonetheless a standard-of-care anesthetic in many clinical scenarios. The Food & Drug Administration (FDA) approved form of ketamine for anesthesia, which is also known as ketamine hydrochloride or racemic ketamine, is a mixture of two mirror-image molecules (stereoisomers): (S)-ketamine and (R)-ketamine.[2] The Drug Enforcement Administration (DEA) classifies ketamine as a Schedule III drug (ie, an agent with low to moderate risk for physical and psychological dependence).[3]

Ketamine is unique in that it causes dissociative anesthesia—a trance-like state characterized by catatonia, catalepsy, and amnesia, but without full unconsciousness.[2] The dissociative state from ketamine anesthesia is believed to occur because ketamine reduces activity in the thalamus and cortex while stimulating other parts of the limbic system, which together disrupt normal communication between the thalamus and cortex.[4] Because of its unique mechanism of action, ketamine has several advantages as an anesthetic agent. In contrast with other general anesthetics, ketamine does not directly interact with gamma-aminobutyric acid (GABA) receptors, and thus cardiovascular and respiratory functions are preserved, reducing the risk of dangerous drops in blood pressure or low blood oxygen levels during anesthesia. Furthermore, ketamine is highly bioavailable, with a rapid onset of action and a relatively short half-life of about three hours. Ketamine also has bronchodilatory and anti-inflammatory properties, making it ideal for anesthesia in patients with certain types of chronic

lung diseases.[5] Indeed, ketamine has even been used in the past to treat status asthmaticus, a type of severe and life-threatening asthma attack.[6]

In addition to its anesthetic properties, ketamine has also been shown to exert analgesic and antidepressant effects through several different mechanisms. Research suggests that ketamine can reduce the transmission of pain signals in the spinal cord, which helps lower pain sensitivity.[7,8] Furthermore, ketamine also affects brain signaling pathways involved in mood regulation: by blocking certain NMDA receptors in the hippocampus, ketamine increases activity α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which supports neuronal signaling and improves the brain's ability to adapt. These properties are believed to underlie the rapid antidepressive effects of ketamine.[9] Importantly, studies have shown that (*S*)-ketamine has about a 3-fold higher affinity for the NMDA receptor than its mirror-image molecule, (*R*)-ketamine, which led to the evaluation and eventual approval of isolated (*S*)-ketamine (esketamine) in a nasal spray formulation for treatment-resistant depression and major depressive disorders with acute suicidal ideation or behaviors.[2,10]

Off-Label Ketamine Use

Regular ketamine, which is a mixture of the (*S*)- and (*R*)-ketamine molecules, is used at subanesthetic doses as an off-label treatment for acute and chronic pain management and, more recently, depression. When compared with opioids for the management of acute pain, ketamine is associated with similar or even greater efficacy and less nausea and vomiting.[11,12] Ketamine can also provide short-term pain relief for patients with certain chronic pain syndromes (ie, spinal cord injury pain and chronic regional pain syndrome [CRPS]), ranging from days to weeks of relief depending on the condition being treated and the dosing schedule used.[13] In patients with depression, ketamine has been shown to rapidly reduce depressive symptoms and, with continued dosing, decrease the risk for relapse.[14]

The effects of ketamine are dose dependent. When used for anesthesia, intravenous (IV) ketamine is typically administered at doses of 1 to 4.5 mg/kg, with an average dose of 2 mg/kg. In contrast, ketamine's analgesic and antidepressive properties are seen at lower doses, typically between 0.1 and 0.5 mg/kg.[13,15,16] Although the precise dosing equivalent between IV ketamine and intranasal esketamine is not well established, it has been estimated that the FDA-approved esketamine dose for depression (56 mg) approximates 0.5 mg/kg IV ketamine.[14] Despite the lower doses of ketamine used for analgesia and depression, this intervention is not without risks. Subanesthetic doses of ketamine are associated with dissociative and psychomimetic symptoms, including hallucinatory effects, along with memory impairment. Furthermore, ketamine stimulates the sympathetic nervous system, which can lead to rapid heart rate, hypertension, and increased cardiac output.[17] As such, guidelines recommend careful monitoring by an appropriately trained health care provider during ketamine administration for pain or depression, with more intensive monitoring recommended at higher dosages or for patients with risk factors for adverse outcomes.[13,15,16]

Over the past several years, rising public interest in ketamine has led to the proliferation of so-called ketamine clinics, which offer off-label ketamine treatment for patients with depression and neuropathic pain. Studies have shown that these clinics can provide much-needed relief for patients suffering from treatment-resistant depression or refractory neuropathic pain.[18,19] However, in addition to treating evidence-based conditions with ketamine, many clinics also offer ketamine for conditions with limited or no supporting evidence, such as obsessive-compulsive disorder, rheumatoid arthritis, and Lyme disease.[20,21] More than 1500 ketamine infusion clinics exist in the United States, with annual revenue estimated at nearly $3.8 billion.[22] Oftentimes, clinics advertise off-label ketamine with misleading or even false claims that are not subject to FDA scrutiny, creating a "direct-to-consumer, profit-driven environment aimed at potentially vulnerable populations."[21] Because the off-label use of ketamine in these clinics is almost never covered by insurance, the vast majority of patients attending these clinics are paying cash, with the advertised cost per infusion ranging from $360 to $3000.[20,23]

Another issue engendered by the rise in ketamine clinics is the increase in the use of compounded ketamine; data from Rhode Island indicate that more than 90% of ketamine prescriptions in the state between 2017 and 2023 were filled by compounding pharmacies.[23] Compounded ketamine is not manufactured under the same FDA approval and oversight standards as commercially available products. This means the quality, strength, and purity of compounded formulations may vary from

one pharmacy to another. To address the rise in compounded ketamine and the associated risks, the FDA has issued multiple statements for health care providers and the general public.[24,25] First, in 2022, the FDA issued an alert regarding the lack of safety data for compounded intranasal ketamine for the treatment of psychiatric disorders.[24] In 2023, the FDA issued a broader warning regarding the use of other compounded ketamine products, including oral and sublingual dosage forms (eg, lozenges, lollipops), which were being offered for an increasingly wide range of disorders.[25] In these press releases, the FDA emphasizes the differences between the FDA-approved agents (intranasal esketamine and IV ketamine hydrochloride) and the compounded forms of ketamine. These and other differences between ketamine, esketamine, and compounded ketamine are summarized in Table 1. For example, esketamine was subject to an extensive phase 3 clinical trial program and subsequent regulatory scrutiny to establish safety, efficacy, potency, and quality, while

Table 1

Comparison of Ketamine and Esketamine Formulations[14,28-30]

Characteristics	Ketamine hydrochloride (Ketalar)	Compounded ketamine	Esketamine (Spravato)
Route of administration	IV or IM	Oral, sublingual, or intranasal	Intranasal
Molecular composition	Racemic mixture	Racemic mixture	(S)-ketamine
Bioavailability	~90%-100%	~10%-50% (significant differences depending on route of delivery, devices, and solutions)	~50%
Regulatory considerations			
FDA-approved indication	Anesthesia	None	TRD or MDD with acute suicidal ideation or behavior
Preapproval evaluation	Safety and efficacy at indicated doses for moderate sedation	N/A	Safety and efficacy at indicated doses for TRD and MDD
Post marketing surveillance	Mandatory reporting of AEs to FAERS	N/A	Mandatory reporting of AEs to FAERS
Warnings and precautions in labeling	• Hemodynamic instability • Emergence reactions • Respiratory depression • Risks of ketamine hydrochloride injection alone for procedures of the pharynx, larynx, or bronchial tree • Pediatric neurotoxicity	N/A	• Sedation[a] • Dissociation[a] • Respiratory depression[a] • Abuse and misuse[a] • Suicidal thoughts and behaviors[a] • Increased blood pressure • Cognitive impairment • Impaired ability to drive and operate machinery • Embryo-fetal toxicity
REMS restrictions	N/A	N/A	• Health care setting and pharmacycertification • Patient enrollment • Pretreatment patient counseling • Supervision during administration • Monitoring for ≥2 hours after administration • Prescriber onsite during administration and monitoring

[a]Boxed warning

AE, adverse event; FAERS, FDA Adverse Event Reporting System; FDA, Food & Drug Administration; IM, intramuscular; IV, intravenous; MDD, major depressive disorder; N/A, not applicable; TRD, treatment-resistant depression

compounded ketamine has not been evaluated beyond small clinical trials and case studies.

Furthermore, esketamine can be dispensed and administered only via a Risk Evaluation and Mitigation Strategy (REMS) program, which mandates administration in a certified health care setting followed by at least 2 hours of patient monitoring for safety.[24] In contrast, compounded ketamine is often prescribed for unsupervised home use and may even be prescribed and dispensed entirely online via telehealth practices.[24-26] Even at subanesthetic dosages, home use of ketamine is not recommended due to the established risks of dissociative events, psychomimetic symptoms, respiratory depression, and blood pressure elevation.[25] Additionally, although data regarding the abuse and diversion of compounded ketamine are limited, more than one-half of surveyed adults using at-home ketamine therapies either purposely or accidentally used more than the prescribed dose.[27]

Without supervision and immediate life-saving care, ketamine overdoses can be serious or even fatal: in April 2023, the FDA described a case in which a person receiving at-home ketamine therapy experienced severe respiratory depression. Toxicology reports revealed that the patient, who was receiving ketamine for posttraumatic stress disorder, had ketamine concentrations at nearly twice the expected levels typical of anesthetic doses of ketamine.[25] Only 6 months later, the risks of at-home ketamine use were again brought to the attention of the public when *Friends* actor Matthew Perry died from the "acute effects of ketamine," which he was receiving at freestanding ketamine clinics and through illicit sources.[31] Another issue with at-home ketamine use is that it may not be as effective as ketamine delivered in a clinic setting by a licensed health care provider. For example, the studies supporting esketamine evaluated this agent as an add-on to patients' current oral antidepressant therapies, and the FDA-approved indication requires that patients continue receiving an oral antidepressant. Furthermore, most of the studies supporting off-label ketamine for depression have shown the most effectiveness when it is delivered in combination with cognitive behavioral therapy.[22,32] And yet, almost one-half of patients receiving ketamine (47%) are doing so unsupervised in their homes.[22]

OVER THE PAST SEVERAL YEARS, RISING PUBLIC INTEREST IN KETAMINE HAS LED TO THE PROLIFERATION OF SO-CALLED KETAMINE CLINICS, WHICH OFFER OFF-LABEL KETAMINE TREATMENT FOR PATIENTS WITH DEPRESSION AND NEUROPATHIC PAIN.

Medical Regulation of Ketamine

The current off-label ketamine environment manages to subvert federal and state regulations intended to ensure patient health and safety. Although the FDA tightly regulates direct-to-consumer marketing by pharmaceutical companies, the rules and regulations governing drug advertising were developed well before the onslaught of online advertising and telehealth. Furthermore, the FDA does not regulate the practice of medicine or medical services and therefore cannot prevent HCPs from offering an approved product for off-label use. The DEA, in collaboration with the Department of Justice, has recently prosecuted health care providers for crimes related to ketamine, including illegal administration, distribution, possession, and fraudulent billing.[33,34] However, the DEA's actions are largely reactive; proactive regulations could possibly protect patients and providers amidst the unprecedented rise in ketamine clinic popularity.

It is the responsibility of states to regulate the practice of medicine, but few states have enacted regulations specific to the off-label use of ketamine in freestanding and telehealth clinics. This has led many experts to compare the explosion of ketamine clinics to the "wild west." The lack of regulatory oversight represents an opportunity to explore options for taking action among state medical regulators, particularly amidst the ongoing unmet need for effective treatments for refractory depression and pain. Regulations may be helpful for all the stakeholders in the off-label ketamine marketplace, including distributors, compounding pharmacies, clinics, and providers themselves. The details provided in this article are intended to help address the multifaceted concerns of all these stakeholders, from physiological, clinical, and logistical perspectives.

Prescribing and Dispensing Ketamine

At this time, any clinician who is licensed to prescribe a DEA Schedule III substance can prescribe and administer ketamine, regardless of their medical specialty. In contrast, esketamine

can only be administered by providers who are licensed in mental health care, primary care, and internal medicine. To reduce misuse of off-label ketamine, many of the largest ketamine distributors require physicians who are purchasing ketamine for psychiatric use to either be licensed in psychiatry or provide robust proof of mental health training or collaboration. It is reasonable to require compounding pharmacies to consider similar efforts to reduce inappropriate use. Additionally, esketamine cannot be dispensed directly to patients and, instead, certified pharmacies must dispense the drug directly to the certified health care facility. Similarly, compounding pharmacies should take caution by dispensing ketamine directly to patients to reduce the rates of risky, unsupervised use.

Regulatory efforts can also contribute to the safe prescribing of off-label ketamine. For example, in Alberta, Canada, medical regulatory authorities require psychedelic-assisted therapy, including ketamine treatment, to be prescribed by a licensed psychiatrist or a physician who is in consultation with a psychiatrist.[35] Although these regulations help restrict the prescribing of ketamine for mental health disorders to physicians with appropriate credentials, no such limitations have yet been instituted for the off-label use of ketamine outside of psychedelic-assisted therapy (eg, for pain or other conditions).

Indications and Risk Management

Clinics that prescribe and administer off-label ketamine for long-term use (eg, for chronic pain or depression) should be required to adhere to standard risk management practices as part of state efforts to regulate ketamine prescribing. These risk management programs can be modeled after the prescription monitoring programs used to regulate and monitor opioid prescribing. At minimum, it is reasonable to designate ketamine as a drug of concern for tracking in the state prescription drug monitoring program (PDMP), which will allow prescribers to identify cases of "doctor shopping," in which patients obtain overlapping prescriptions from different providers with the intent of misusing, abusing, or diverting the substances. In Canada, ketamine has been added to PDMPs in certain provinces, providing pharmacists, clinicians, and regulatory bodies with access to both patient and prescriber profiles related to controlled substances. In Alberta, the program regularly evaluates records to identify patients who are doctor shopping and inform prescribers.[36]

Another advantage of PDMP queries prior to the prescription of ketamine is that they can help identify patients who are on other controlled substances, which could lead to oversedation. In particular, patients who are on high doses of opioids and those receiving benzodiazepines are at elevated risk for adverse events. An informed risk-benefit discussion is warranted with these patients, including a discussion of alternative treatment options.

Ketamine clinics should also be required to document that they are following best practices prior to prescribing ketamine. First, indications for prescribing should be evidence based (eg, treatment-resistant depression, neuropathic pain), and ketamine should only be pursued after standard-of-care options have been trialed and deemed ineffective or inappropriate. Furthermore, providers should engage in a full informed decision-making discussion with patients, which should, at minimum, include disclosure of the off-label nature of treatment, ketamine addiction and abuse potential, the risks of compounded treatments (if using), and alternative treatment options. In Canada, the medical regulatory authorities for several provinces have developed regulations for community-based off-label ketamine use, which include the requirement for the documentation of informed consent in patient medical records.[37]

CLINICS THAT PRESCRIBE AND ADMINISTER OFF-LABEL KETAMINE FOR LONG-TERM USE (EG, FOR CHRONIC PAIN OR DEPRESSION) SHOULD BE REQUIRED TO ADHERE TO STANDARD RISK MANAGEMENT PRACTICES AS PART OF STATE EFFORTS TO REGULATE KETAMINE PRESCRIBING.

Prior interventions and the contents of the informed decision-making discussion should be documented in the patient's medical records. Baseline and follow-up measures of treatment response, such as with the Patient Health Questionnaire 9 (PHQ-9) or the numeric rating scale for pain, should be obtained, and clinicians should consider discontinuing ketamine therapy for non-responders. Patients should also be screened for the risk of misuse and abuse with a formalized assessment such as the Opioid Risk Tool or other similar tools or question-

naires. For patients at elevated risk of abuse, the appropriateness of ketamine therapy should be weighed carefully alternative options.

Administration and Safety

One of the major risks of the recent proliferation of freestanding ketamine clinics is the lack of onsite physician supervision at many of these sites. In one recent survey, about one-third of ketamine clinics did not have a physician as part of their treatment team.[38] And yet, major psychiatric and pain management societies recommend that ketamine infusions should only be performed under the care of a licensed physician with Advanced Cardiac Life Support (ACLS) certification. Furthermore, when off-label ketamine is being used at higher doses (eg, >0.5 mg/kg for chronic pain), supervising physicians should also meet American Society of Anesthesiologists (ASA) requirements for the administration of moderate sedation.[13,39,40] Additional training in ketamine dose titration, recognizing and responding to adverse events, and the pharmacology of ketamine should be mandated for all clinical staff, particularly for the nurses and other clinicians responsible for ketamine administration and patient monitoring.

During ketamine administration, monitoring for airway protection, cardiovascular stimulation, drug-drug interactions with concomitantly administered medications (eg, midazolam), and adverse events such as psychomimetic symptoms is required to ensure patient safety. This should, at minimum, include hemodynamic parameters (eg, blood pressure and heart rate), respiratory parameters (eg, pulse oximetry), and sedation/consciousness levels. All clinics should be equipped with the personnel and equipment necessary for resuscitation in case of serious adverse events. Before beginning the infusion, clinicians should ensure patients have not ingested any food or fluids recently, and after the infusion, patients should be monitored until they meet prespecified discharge criteria.

Conclusions

Ketamine is an important—and lifesaving for some—treatment that plays a critical role in the management of conditions that have failed to respond to standard-of-care interventions. For those with treatment-resistant depression, acute suicidality, or certain types of chronic pain, ketamine can provide rapid symptom relief. As with all medical interventions, however, ketamine use is associated with risks, and regulators are responsible for ensuring that providers take those risks seriously. To ensure patients are receiving high-quality health care, state medical regulations may be needed to promote safe ketamine prescribing, dispensing, administration, monitoring, and risk management. The goal of these regulations is not to limit access to ketamine but instead to ensure that patient safety remains at the forefront of all health care interactions at freestanding ketamine clinics.

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