

Off-Label Use of Ketamine: A Challenging Drug Treatment Delivery Model With an Inherently Unfavorable Risk-Benefit Profile

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 On behalf of the ACCP Public Policy Committee

Intravenous racemic ketamine is being promoted and used off-label for several psychiatric conditions and other disorders. Off-label use of drugs is prescribing outside their US Food and Drug Administration (FDA)-approved product label. The FDA act of 1938, and the Kefauver-Harris Amendment of 1962, requires that drugs are shown to be safe and effective to gain approval and for commercialization; the manner in which approved drugs are used is dictated by the (FDA-endorsed) product label. Obtaining FDA approval is time consuming, expensive, and based on stringent review of a plethora of data from scientific and clinical investigations.¹ Off-label drug use applies to use for a disease that it is not approved to treat, administered in a manner different than the approved dose, change in formulation, or use in populations different than in which approval was granted. While approval of drugs that are safe and effective rests solely with the FDA and has jurisdiction and enforcement authority over commercial promotion of off-label use, the FDA does not regulate the practice of medicine and hence the off-label use of drugs by physicians.¹ However, it is the position of the FDA that “if physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.”²

Ketamine, a Schedule III drug derived from phencyclidine, consisting of R- and S-isomers,³ was approved by the FDA in 1970 as a rapid-acting general anesthetic for intravenous (IV) or intramuscular administration (dose range, 1–4.5 mg/kg and 6.5–13 mg/kg, respectively), with dose titration according to requirements of individual patients. Ketamine produces “dissociative anesthesia”; adverse reactions include elevation of blood pressure and pulse rate, and severe depression of respiration may occur with rapid IV administration, and is only for use by medical

personnel experienced in the use of anesthetics and maintenance of airway/respiration, with availability of resuscitative equipment.⁴ The drug’s abuse potential and recreational use is recognized; healthy subjects reported feeling “high” at a subanesthetic dose (0.5 mg/kg per 40-minute IV), and a lower dose (0.1 mg/kg) induced mild euphoria.⁵ With a low plasma protein binding, ketamine has a large volume of distribution and is rapidly distributed into the brain.³ Ketamine undergoes extensive hepatic metabolism by cytochrome P450 enzymes (3A4, 2B6).⁶ Blockade of the N-methyl-D-aspartate receptor is responsible for the anesthetic, analgesic, antidepressant, and altered psychotomimetic effect of ketamine, with the S-isomer having several-fold higher affinity/potency for the phencyclidine site of the receptor than R-ketamine (and the racemic mixture).^{3,4} These properties make racemic ketamine more likely to show drug-drug interactions that could increase the safety risk when used in an off-label manner and outside the purview of a patient’s primary care physician. Furthermore, the safety aspects raise serious concerns with off-label use of ketamine in law enforcement situations.⁷

Intravenous ketamine (at a typical dose of 0.5 mg/kg per 40 minutes), while lacking anesthetic effects, is being used in patients with major depressive episodes. However, this treatment mode has not been subjected to FDA review for on-label use for any psychiatric indication, and is without formal postmarketing surveillance regarding its safety and efficacy.⁸ As previously reported, some healthy subjects were unresponsive to verbal stimuli following IV ketamine,⁹ and at a dose of 0.5 mg/kg over 40 minutes, 30% of patients with

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depression had transient increases in systolic and diastolic blood pressure exceeding 180/100 mm Hg or heart rates exceeding 110 beats per minute.¹⁰ In view of these safety risks, it is suggested that a licensed physician with Advanced Life Support certification should administer this Drug Enforcement Administration Schedule III drug, and that there is on-site clinician evaluation of behavioral risks, including suicidal ideations.⁸

The FDA approved the S-enantiomer of ketamine (esketamine [Spravato]) in 2019, as nasal spray, with Fast Track and Breakthrough Therapy designations.¹¹ Esketamine is the first approval for chronic use, specifically for treatment-resistant depression (and not as an anesthetic agent), and was further approved in 2020 for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior (and not any other indications). Because of the risks of serious adverse outcomes, Spravato is available only through a restricted distribution system under a Risk Evaluation and Mitigation Strategy (REMS) that specifies standards for health care settings (both inpatient and outpatient) and pharmacies and health care professionals administering the drug.¹² Under the REMS program, certified inpatients and outpatients must be counseled by health care providers regarding the risks of Spravato. Because of the possibility of delayed or prolonged sedation, risk of dissociation, and increases in systolic and diastolic blood pressure, patients should be monitored for at least 2 hours after each treatment. Risk vs benefit aspects should be considered when prescribing Spravato in patients with cardiovascular and cerebrovascular conditions.¹² Currently, it is not known if Spravato is used off-label. The REMS program is active, and the FDA is still monitoring compliance to the program with the sponsor. These safeguards underscore the importance of ensuring patient safety by the FDA in view of the risk-benefit profile of the drug. While racemic ketamine was approved by the FDA in 1970 as a single-use anesthetic agent, it has not been approved for any other indication nor for chronic use.

The critical difference between the use of Spravato in a clinical setting vs ketamine clinics is in the product used: ketamine clinics use IV racemic ketamine as single or repeat infusions. Before and after the approval of Spravato, numerous ketamine clinics opened and offered IV ketamine-assisted therapy for psychiatric and a variety of conditions such as migraines, major anxiety, neuropathic pain, posttraumatic stress disorder, pain syndromes, postpartum depression, obsessive-compulsive disorder, rheumatoid arthritis, restless leg syndrome, Lyme disease, and tinnitus. Such therapeutic claims, with limited scientific evidence, have created a direct-to-consumer profit-driven environment, aimed at

potentially vulnerable populations, and without proper regulatory and legislative oversight.¹³ In the United States, such clinics have increased exponentially since 2015, thus underscoring the magnitude of the issue regarding off-label uses of this Schedule III drug. Due to limited data, lack of training guidelines for dosing, and safety aspects (eg, blood pressure, heart rate elevations at an antidepressant dose of 0.5 mg/kg IV per 40 minutes), there are serious concerns regarding the off-label use of IV ketamine. This is compounded by the inherent safety risk of using an anesthetic agent. Symptoms unique to overdose or rapid infusion may include respiratory depression, apnea, hypotension, bradycardia, myocardial infarction, seizure, stupor, coma, and laryngospasm.^{14,15} Additionally, there are no medications approved by the FDA to treat a ketamine overdose.

IV ketamine therapy in an outpatient clinic and off-label promotion is also unique because the clinics do not seek regulatory approval for the claimed indications. Ketamine clinics are ostensibly medical facilities, but beyond FDA jurisdiction and oversight, and fall under individual state licensure. Additionally, their relationship to compounding pharmacies is unknown. In contrast to ketamine clinics, it is emphasized that off-label use of ketamine by physicians based on treatment plan for patients is appropriate and is consistent with the FDA position regarding this aspect. It is noteworthy that the setting of ketamine clinics is very different from the migraine clinics that were using topiramate (Topamax) off-label before its approval. In that setting, the relationship was between physicians and patients to provide the best possible integrated management of their disease, while active clinical trials were ongoing.¹⁶ In the current setting for ketamine clinics, there is a disintermediation or a complete lack of relationship between a competent health care provider treating a patient for other specific disease(s) and the clinics promoting and administering ketamine. Additionally, and quite differently, Topamax does not have acute life-threatening cardiorespiratory effects as for racemic ketamine, and its FDA approval for seizures is consistent with today's standards for proof of safety and effectiveness. The risk-benefit aspects and lack of an inclusive disease management program does not support the off-label use of racemic ketamine in ketamine clinics.

The position of the American College of Clinical Pharmacology (ACCP) is that the use of racemic ketamine in depression and other disorders as advertised by ketamine clinics is true off-label use in the most serious manner: (1) for disease conditions that are not approved for treatment; (2) administered in a manner that is different than the approved dose; (3) for populations different than the one in which approval was granted; (4) does not fall into the individual

medical practice (patient-doctor relationship) category and is unregulated by the FDA because the clinics themselves are promoting the off-label use of racemic ketamine infusions, increasing the risk to patients; and (5) lack of published guidelines or recommendations to clinic staff for IV ketamine administration and titration of doses lower than for anesthesia, and training in cardiovascular and respiratory emergencies.

To address these serious concerns that impact patient safety in the face of unsubstantiated therapeutic claims, the ACCP recommends (1) obtaining dose/concentration-response data for relevant indications (eg, via well designed pharmacokinetic/pharmacodynamic trials) and that such information be made publicly available (via National Institutes of Health/National Institute of Mental Health–sponsored programs); (2) implementation of standardized dosing, training, and safety monitoring with data collection (via state-driven mandate); (3) periodic database searches of the FDA Adverse Event Reporting System to monitor the incidence of the known and emergent adverse reactions caused by ketamine (under FDA purview); (4) implementation of disclosures to patients of the risks and safety profile of ketamine (documented by the medical personnel of the clinics); and (5) a strong linkage of ketamine treatment to primary care physicians to follow potential long-term side effects, drug interactions, and other relevant aspects as part of a comprehensive treatment plan for individual patients, including mental health management (by the clinics under a state mandate).

Separately, the ACCP supports supervised dosing of Spravato as intended by the FDA. Spravato is an important approval by the FDA and advances comprehensive mental health care. The REMS program is similar to the “chemotherapy” model in oncology for outpatient therapy implemented in a well-supervised setting with patient support. Such clinics and settings, if monitored and regulated, represent an essential aspect of chronic disease care.

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Conflicts of Interest

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Disclaimer

The opinions expressed in this article are those of the authors on behalf of the American College of Clinical Pharmacology and should not be interpreted as the position of the entities or institutions at which the authors are employed.

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