

Regulating Ketamine Use in Psychiatry

Lisa Harding, MD

J Am Acad Psychiatry Law 51:320–25, 2023. DOI:10.29158/JAAPL.230040-23

Key words: esketamine; ketamine; regulation

Ketamine is a dissociative anesthetic that has gained attention in the field of psychiatry because of its unique mechanism of action and potential for treating treatment-resistant psychiatric disorders. It has been used off label for decades to treat depression, anxiety, and chronic pain. One of the most significant advancements has been the U.S. Food and Drug Administration's (FDA) approval of esketamine, the S enantiomer of racemic ketamine, for treatment-resistant depression (TRD) and depression with acute suicidal ideation. Unlike traditional antidepressants, which can take several weeks to start working, esketamine and ketamine can begin to alleviate symptoms within hours of administration.^{1,2} Esketamine is also the only antidepressant of its kind to be studied and approved by the FDA for depressive symptoms in a suicidal population.

Over the last five years there has been increased tension among medical providers regarding who is best suited to deliver care with ketamine and esketamine.³ Although the use of ketamine for depression and other psychiatric conditions has gained increasing attention, there is limited research available to support its use in many of the disorders for which it is used off label. Despite this lack of evidence, ketamine clinics have emerged as a popular alternative for patients who have not responded to traditional treatment options. In addition, the classification of the drug as a Schedule III (CIII) controlled substance and its potential for abuse and dependence raise significant concerns about its safety and appropriate use in medical settings.

Dr. Harding is a psychiatrist in independent practice in Connecticut and is Assistant Clinical Professor of Psychiatry, Yale University School of Medicine, New Haven, CT. Address correspondence to: Lisa Harding, MD. E-mail: dr.lisa.harding@gmail.com.

Disclosures of financial or other potential conflicts of interest: Dr. Harding reports that she a former Vice President of the American Society of Ketamine Physicians, Practitioners and Psychotherapists, and receives compensation for being a member of advisory panels on mood disorders for Janssen Neuroscience, Compass Pathways, and Takeda Pharmaceuticals.

There is a pressing need for increased research and regulatory oversight into the potential risks and benefits of ketamine as a treatment for multiple psychiatric conditions. As the off-label use of ketamine for psychiatric disorders evolves as a therapeutic option, it is imperative that regulatory authorities promptly establish guidelines and regulations to promote its safe and effective use.

This editorial examines the current state of knowledge regarding the use of ketamine and esketamine for psychiatric disorders and presents a framework for thinking through the challenges and opportunities for regulating the use of ketamine in psychiatry.

Clinical Trials and Evidence-Based Use

The available clinical trials offer early data regarding the safety and efficacy of the use of ketamine for psychiatric disorders, although the quality of the evidence regarding dosing and routes of administration varies.⁴ The quality of the evidence should be considered in concert with the need to balance both the safety and potential benefits of innovative treatments when determining the usefulness of ketamine for particular psychiatric disorders. Regardless of condition, based on the available evidence these treatments cannot be considered first-line therapies. There are no widespread data on their use as monotherapies, and thus far there have been no head-to-head clinical trials to evaluate ketamine versus esketamine in the treatment of any psychiatric disorder.

The antidepressant effects of both ketamine and esketamine have been studied extensively in recent years, with numerous randomized, controlled trials (RCTs) and meta-analyses supporting their efficacy in TRD. A meta-analysis of 11 RCTs found that ketamine had a significant and rapid antidepressant effect compared with placebo.⁵ For esketamine, a phase 3, double-blind, active-controlled, multicenter study showed clinically meaningful improvement in

the esketamine plus antidepressant arm.² Ketamine has limited data in other psychiatric disorders, including bipolar depression, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD).^{6–8} Ketamine's off-label use in these psychiatric disorders has been controversial, and its use should be limited to administration by experts in interventional psychiatric care. Providing patients and their caregivers with information on the current evidence supporting the use of ketamine should be an integral part of the process of obtaining informed consent.

Licensing and Prescribing

Licensing and regulatory control are currently limited but will be essential to ensure the future appropriate use of ketamine for psychiatric conditions. Currently, despite sharing similarities in safety and efficacy, ketamine and esketamine differ vastly in their regulatory status. Although both are CIII controlled substances in the United States, esketamine has gained FDA approval for use in treatment-resistant depression with strict administration regulations given its potential for abuse and dissociative side effects. In contrast, the use of ketamine in psychiatry remains largely unregulated in most states because it has FDA approval only as an anesthetic agent, and off-label use for most medication remains at the discretion of the provider.

Ketamine can be administered by practitioners who are licensed to prescribe CIII substances within medical specialties, including anesthesiology, psychiatry, emergency medicine, primary care, and internal medicine.^{9–12} Esketamine has been restricted to administration by practitioners who are licensed to prescribe CIII substances within mental health care, primary care, and internal medicine.

There are investigative reports by journalists across the country on the proliferation of ketamine clinics and the lack of regulation.^{13,14} This public scrutiny has led to some positive changes. For example, several of the largest distributors of ketamine have either stopped selling ketamine for psychiatric use to non-psychiatric providers or now require robust evidence of training in mental health or proof of a collaborative relationship with a mental health provider to purchase ketamine for psychiatric use. To circumvent this requirement, some providers have engaged with compounding pharmacies to provide ketamine in various forms, prompting the FDA to issue an alert to remind

providers and patients that there are no data to support dosing conversion between esketamine nasal spray and compounded ketamine nasal spray.¹⁵ A potential recommendation for regulating compounding pharmacies that provide ketamine to practitioners for psychiatric purposes is to implement clear and standardized guidelines that are similar to the standard used by well-established distributors. Additionally, there could be regulations in place to monitor and track the distribution and administration of compounded ketamine to ensure that it is being used appropriately and safely. Such regulations may help to mitigate the potential risks associated with the use of compounded ketamine and ensure that patients receive safe and effective treatment.

Risk Management and Monitoring

Another key aspect of regulating ketamine for psychiatric use is developing strategies for managing and monitoring the risks associated with its use. In the current landscape, the two treatments differ vastly in the delivery of care models.

Esketamine cannot be dispensed directly to patients. The FDA required a Risk Evaluation and Mitigation Strategy (REMS) to manage known or potential risks associated with esketamine. Patients are required to remain at a REMS-certified treatment center for two hours, and the treatment facility is required to submit treatment data after every treatment. As a result, the risk of diversion of esketamine remains relatively low. Continuous data collection from an ongoing, open-label safety study,^{16,17} has been instrumental in providing crucial insights into the safety profile of esketamine. These data not only inform the FDA but also guide health care practitioners in their decision-making process. Conversely, the absence of such universal long-term outcome data for ketamine usage raises several questions about its safe and effective use, leaving its long-term efficacy and safety profile uncertain.

Further, patients' use of ketamine for any medical purpose does not appear in any state's prescription drug monitoring program. There is no oversight or formal data collection system for dosing or treatment outcomes.¹⁸ As a result, several safety concerns have been raised regarding its use, particularly with respect to its potential for abuse, dependence, and diversion.¹⁹

Patient Access and Affordability

Treating psychiatric patients with ketamine and esketamine is still a developing and nuanced skill in psychopharmacology. A psychiatric assessment to identify the appropriate patient should be completed by a mental health expert who understands the clinical administration of both ketamine and esketamine and their indications. Patients must undergo a thorough medical evaluation to ensure that they do not have any preexisting medical conditions that may interact negatively with the proposed treatment. Moreover, certain medical conditions can limit or completely contraindicate the use of ketamine or esketamine, making it essential to assess a patient's medical history and current health status. Patients with certain conditions, such as aneurysmal vascular disease, liver impairment, or kidney diseases, for example, may require lower doses of medications or require closer monitoring to avoid complications. The collaborative treatment team should determine whether the benefits outweigh the risk of treatment.

Patient access to ketamine for psychiatric use and the affordability of treatment is perhaps the most important aspect of its regulation. Regulatory decisions will affect the availability and cost of treatment and how policymakers work to ensure that patients have access to these innovative therapies regardless of their income or insurance status. This risk is particularly concerning given a systematic literature review demonstrating that prescribers were more likely to recommend novel drug therapies for patients with higher income levels or with private insurance and were less likely to recommend novel drug therapies for African-American or Hispanic patients.²⁰

It is important that we ensure equitable access to this treatment, especially given the well-documented racial disparities in mental health care. Studies have shown that Black individuals with depression are less likely to receive adequate treatment compared with their White counterparts, which can contribute to higher rates of suicide within this population.²¹ In a subgroup analysis with esketamine, safety and efficacy results observed in Black or African-American patients were consistent with the overall patient population studied.²²

Patients seeking ketamine treatment for psychiatric disorders face a significant financial burden, needing to pay out of pocket for treatment because insurance coverage for this type of therapy is often limited or nonexistent. As a result, access to ketamine treatment

remains a significant financial challenge, particularly for underserved and marginalized communities who may not have the resources to pay for it. Esketamine, although covered by most insurance plans, has only two FDA-approved indications (treatment-resistant depression and major depressive disorder with acute suicidal ideation), thus limiting coverage for any off-label indication.

Although other forms of ketamine may be less expensive than intravenous or intranasal esketamine, it is important to acknowledge that these alternative, less-expensive formulations have not been thoroughly studied for the treatment of depression or other psychiatric disorders, and its use is not considered a standard of care. Patients, regardless of their socioeconomic background, should receive the best evidence-based treatments that adhere to the highest standard of clinical practices. It is essential that health care policies and systems prioritize equitable access to care for all patients.²³

Esketamine and Ketamine in Corrections

A systematic review and meta-analysis published in *Lancet Psychiatry* in 2016²⁴ showed that the prevalence of depression among prisoners was found to be 22 percent, significantly higher than the general population. The findings highlight the need for increased mental health services and interventions in correctional facilities to address the high rates of depression among inmates.²⁴ Esketamine and ketamine are regarded as treatment options within the Veterans Affairs (VA)/Department of Defense (DoD) guidelines for treatment-resistant depression.²⁵ Such treatments ought to be available to incarcerated individuals and other forensic populations.

The novel mechanism of delivery of esketamine has not been explored as an option for treatment-resistant depression in this population. Understandably, intravenous or intramuscular ketamine may present barriers to implementation and delivery in a correctional setting, but other models involving interventional care with medical illness, such as chronic kidney disease, have been successful.^{26,27} This established practice raises the possibility that similar goals could be accomplished for interventional psychiatric treatments in this population.

There is also the opportunity for examination of the evidence and confronting the stigma of the use of ketamine, particularly in the context of treating incarcerated individuals. Ketamine has a low potential for abuse when administered at sub-anesthetic doses, and

Table 1 Dependence Potential of Psychoactive Drug. (Generated from Data Presented in Gable³⁴)

Dependence potential	Psychoactive substance(s)
Very High	heroin
High	nicotine, morphine
Moderate High	cocaine, pentobarbital
Moderate	alcohol, ephedra, flunitrazepam
Moderate Low	caffeine, marijuana, MDMA, nitrous oxide
Low	ketamine
Very Low	LSD, mescaline, psilocybin

it also has a lower active/lethal dose ratio and dependence potential (see Table 1).^{28,29} The development of regulatory mechanisms for the use of ketamine may address the concerns of correctional health and custody administrators and in turn present an opportunity for improved access to care and treatment, expanding the effective clinical tools available for correctional psychiatrists.

Ketamine and the Legal Landscape

Despite having the authority to regulate the manufacture, distribution, and dispensing of ketamine, the ability of the Drug Enforcement Administration (DEA) to control how the drug is used in medical settings, such as ketamine infusion clinics, is significantly limited. The ownership and operation of ketamine clinics is generally influenced by the Corporate Practice of Medicine (CPOM) doctrine.³⁰ The CPOM doctrine has a significant impact on the financing, development, management, and marketing of ketamine, which is increasingly important as more clinics and patients make use of the drug. Ketamine is not yet approved for use in treating psychiatric disorders, creating a gray area in which the legal status of use of the drug for this purpose is not entirely clear. The scarcity of psychiatrists who offer ketamine treatment has led patients to seek alternative care sites, and nonpsychiatrists have stepped in to provide this specialized care.

The American Psychiatric Association (APA) has limited resources to support psychiatrists in their understanding, management, and feasible implementation of established treatments such as ketamine and esketamine, leaving many psychiatrists feeling uncomfortable with treating or referring patients for these treatments. The APA has not revised its depression treatment guidelines since 2010³¹ to include the FDA-approved esketamine, suggesting the urgent need for updated guidance in the field. The APA has, however, published a consensus statement in response to the

unregulated use of ketamine with an aim to provide guidance for the use of ketamine in psychiatry.³² The statement emphasizes the need for careful patient selection and monitoring, as well as the importance of integrating ketamine treatment into a comprehensive treatment plan that includes psychotherapy and other pharmacological interventions.

Lawsuits brought against doctors or manufacturers regarding the administration or distribution of ketamine as an off-label treatment for psychiatric disorders can have significant implications for patient care and the availability of the medication. It is important to consider the emotional and financial toll of litigation and how it may discourage other doctors from considering ketamine as a treatment option, further limiting its accessibility. Balancing patient safety and legal responsibilities requires a nuanced understanding of the complexities of the off-label use of ketamine for psychiatric disorders.

There is also no single set of universally recognized standards and ethics with regard to the use of ketamine for psychiatric conditions. There is a noteworthy proliferation within psychiatry of developing care models for newly emerging psychedelic treatments that have not yet received FDA approval.³³ This proactive approach is perhaps aimed at avoiding a situation similar to what has been observed with ketamine or cannabis, where these treatments have been widely adopted and commercialized before sufficient evidence on their safety and efficacy has been established.

Stigma and Media

Ketamine has been subject to significant stigma, particularly in the context of substance misuse and recreational drug use. It is essential to recognize the potential benefits of ketamine as a treatment option and to understand that its use in a medical setting is different from its recreational use. Health care providers must educate themselves and their patients on the benefits and risks of ketamine.

The portrayal of ketamine in the media also contributes to adverse views held by patients who may be reluctant to accept this treatment despite its therapeutic benefits. The case of Elijah McClain³⁵ raised significant concerns about the use of ketamine in law enforcement and emergency medical settings. Elijah McClain was a young Black man who died in 2019 following the administration of ketamine by first responders during a police encounter in Colorado. The

use of ketamine in this case has been subject to scrutiny, with questions raised about the appropriateness of its use and the training and qualifications of the personnel involved.^{36,37} This case highlights the need for careful consideration of the potential risks and benefits of using ketamine in emergency situations and the importance of ensuring that its administration is carried out safely and appropriately. It is essential that law enforcement and emergency medical personnel are properly trained to recognize and manage medical and psychiatric emergencies and that the use of ketamine is limited to medically appropriate cases.³⁸ The involvement of forensic psychiatrists in the regulatory process of ketamine can provide further expertise and direction on the proper and ethical application of the drug.

Conclusion

The complex psychiatric and ethics considerations regarding the administration of ketamine necessitate a coordinated effort by mental health providers and researchers who work with ketamine to be involved in standardizing regulations and guidelines, to ensure that the medication is prescribed and administered appropriately for psychiatric indications. Failure to do so could not only jeopardize patient safety but also expose providers to significant legal and professional consequences. Clinicians must balance the potential benefits of using ketamine off label to treat depression against the legal and ethics risks associated with doing so.

References

1. Grunebaum MF, Galfalvy HC, Choo T-H, *et al.* Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *Am J Psychiatry.* 2018; 175(4):327–35
2. Popova V, Daly EJ, Trivedi M, *et al.* Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *Am J Psychiatry.* 2019; 176(6):428–38
3. Harrison A. Ketamine providers debate standards of care. *Lucid News* [Internet]; 2021 Mar 22. Available from: www.lucid.news/ketamine-providers-debate-standards-of-care/. Accessed May 7, 2023
4. McIntyre R, Rosenblat J, Nemeroff C, *et al.* Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *Am J Psychiatry.* 2020; 178(5):365–470
5. Newport DJ, Carpenter LL, McDonald WM, *et al.* Ketamine and other NMDA antagonists: Early clinical trials and possible mechanisms in depression. *Am J Psychiatry.* 2015; 172(10):950–66
6. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of Ketamine in bipolar depression: Systematic review and meta-analysis. *J Psychiatr Pract.* 2015; 21(6):427–35
7. Feder A, Parides MK, Murrough JW, *et al.* Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry.* 2014; 71(6):681–8
8. Rodriguez CI, Kegeles LS, Levinson A, *et al.* Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: Proof-of-concept. *Neuropsychopharmacology.* 2013; 38(12):2475–83
9. Abed Faghri NM, Boisvert CM, Faghri S. Understanding the expanding role of primary care physicians (PCPs) to primary psychiatric care physicians (PPCPs): Enhancing the assessment and treatment of psychiatric conditions. *Ment Health Fam Med.* 2010; 7(1):17–25
10. Parikh SV, Lopez D, Vande Voort JL, *et al.* Developing an IV ketamine clinic for treatment-resistant depression: A primer. *Psychopharmacol Bull.* 2021; 51(3):109–24
11. Sanacora G, Schatzberg AF. Ketamine: Promising path or false prophecy in the development of novel therapeutics for mood disorders? *Neuropsychopharmacology.* 2015; 40(2):259–67
12. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol.* 2011; 14(8):1127–31
13. Dodge D. The ketamine cure. *The New York Times* [Internet]; 2021 Nov 4. Available from: <https://www.nytimes.com/2021/11/04/well/ketamine-therapy-depression.html>. Accessed May 7, 2023
14. Dunn L, Snow K. Ketamine clinics for mental health are popping up across the U.S. Does the treatment work? *NBC News Online* [Internet]; 2023 Jan 4. Available from: <https://www.nbcnews.com/health/mental-health/ketamine-clinics-mental-health-are-popping-us-treatment-work-rcna63522>. Accessed May 7, 2023
15. U.S. Food and Drug Administration. FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray. Silver Spring, MD: U.S. FDA [Internet]; 2022 Feb 16. Available from: <https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray>. Accessed May 7, 2023
16. Daly EJ, Trivedi MH, Janik A, *et al.* Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry.* 2019; 76(9):893–903
17. Ochs-Ross R, Wajs E, Daly EJ, *et al.* Comparison of long-term efficacy and safety of esketamine nasal spray plus oral antidepressant in younger versus older patients with treatment-resistant depression: Post-hoc analysis of SUSTAIN-2, a long-term open-label phase 3 safety and efficacy study. *Am J Geriatr Psychiatry.* 2022; 30(5):541–56
18. Burton KW. Time for a national ketamine registry, experts say. *Medscape Psychiatry* [Internet]; 2023 Feb 15. Available from: <https://www.medscape.com/viewarticle/988310>. Accessed May 7, 2023
19. Wilkinson ST, Sanacora G. At-home ketamine: Still a lot to learn. *J Affect Disord.* 2022; 318:150–1
20. Lubl6y . Factors affecting the uptake of new medicines: A systematic literature review. *BMC Health Serv Res.* 2014; 14:469
21. McGuire TG, Miranda J. New evidence regarding racial and ethnic disparities in mental health: Policy implications. *Health Aff (Millwood).* 2008; 27(2):393–403
22. Harding L, Cabrera P, Fu DJ. Long-term safety and efficacy of esketamine nasal spray in black and/or African American adults with treatment-resistant depression: A subgroup analysis of the

- SUSTAIN-3 study. Poster presented at: US Psych Congress; September 17-20, 2022, New Orleans, LA
23. Fradgley EA, Paul CL, Bryant J. A systematic review of barriers to optimal outpatient specialist services for individuals with prevalent chronic diseases: What are the unique and common barriers experienced by patients in high income countries? *Int J Equity Health*. 2015; 14:52
 24. Fazel S, Hayes AJ, Bartellas K, *et al*. Mental health of prisoners: Prevalence, adverse outcomes, and interventions. *Lancet Psychiatry*. 2016; 3(9):871–81
 25. U.S. Department of Veterans Affairs. VA/DoD Clinical Practice Guidelines: Management of Major Depressive Disorder (MDD). Washington, DC: U.S. Department of Veterans Affairs [Internet]; 2022. Available from: <https://www.healthquality.va.gov/guidelines/MH/mdd/>. Accessed May 7, 2023
 26. Murphy M, Ding A, Berk J, *et al*. Kidney disease among people who are incarcerated. *Clin J Am Soc Nephrol*. 2021; 16(11):1766–72
 27. Sankaranarayanan N, Agrawal R, Guinipero L, *et al*. Self-performed peritoneal dialysis in prisoners. *Adv Perit Dial*. 2004; 20:98–100
 28. Swainson J, Klassen LJ, Brennan S, *et al*. Non-parenteral ketamine for depression: A practical discussion on addiction potential and recommendations for judicious prescribing. *CNS Drugs*. 2022; 36(3):239–51
 29. National Center for Drug Abuse Statistics [Internet]. Available from: <https://drugabusestatistics.org/fentanyl-abuse-statistics/>. Accessed May 7, 2023
 30. American Medical Association. Issue brief; corporate practice of medicine [Internet]. Available from: https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/premium/arc/corporate-practice-of-medicine-issue-brief_1.pdf. Accessed May 7, 2023
 31. American Psychiatric Association. Practice Guideline for the Treatment of patients with Major Depressive Disorder, third edition [Internet]; 2010. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed May 7, 2023
 32. Sanacora G, Frye MA, McDonald W, *et al*. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017; 74(4):399–405
 33. Brennan W, Belser AB. Models of psychedelic-assisted psychotherapy: A contemporary assessment and an introduction to EMBARK, a transdiagnostic, trans-drug model. *Front Psychol*. 2022; 13:866018
 34. Gable RS. Acute toxicity of drugs versus regulatory status. In Fish JM, editor. *Drugs and Society: U.S. Public Policy*. Lanham, MD: Rowman & Littlefield Publishers; 2006. p. 149–62
 35. Tompkins L. Here's what you need to know about Elijah McClain's death. *The New York Times* [Internet]; 2022 Jun 25. Available from <https://www.nytimes.com/article/who-was-elijah-mcclain.html>. Accessed May 7, 2023
 36. Wilkinson ST, Sanacora G. Considerations on the off-label use of ketamine as a treatment for mood disorders. *JAMA*. 2017; 318(9):793–4
 37. Hampton DJ. Five officers and medics plead in death of Elijah McClain. *NBC News* [Internet]; 2023 Jan 20. Available from: <https://www.nbcnews.com/news/us-news/five-officers-medics-plead-death-elijah-mcclain-ketamine-rcna66722>. Accessed May 17, 2023
 38. Appelbaum PS. Excited delirium, ketamine, and deaths in police custody. *Psychiatr Serv*. 2022; 73(7):827–9