



The Evolution of Pandemic-Influenced Ketamine Internet Prescribing

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In the past decade, treatment modalities and indications for ketamine, a noncompetitive NMDA antagonist, have shifted from anesthesia to neuromodulation, based on its antidepressant effects. Duman et al. hypothesized that the biochemical mechanisms responsible for ketamine's antidepressant properties were AMPA receptor and NMDA-related glutamergic activity promoting BDNF release, with downstream effects on protein expression and signaling pathways that increase neuronal structural connectivity in the prefrontal cortex. (1) Essentially, ketamine's secondary epigenetic effects generate new neuronal pathways, which may contribute to its therapeutic efficacy in treatment-resistant depression (TRD). (2) Though psychiatrists have used ketamine off-label since its initial approval as an anesthetic in the 1970's, the ketamine enantiomer esketamine received US Food and Drug Administration (FDA) approval for TRD in 2019, formulated as a nasal spray under the brand name Spravato. This stamp of approval sparked the recent expansion of off-label ketamine clinics across the US, providing treatment to patients with chronic pain or psychiatric conditions. Credible clinic appointments consist of licensed healthcare professionals administering either carefully titrated ketamine infusions or intranasal esketamine. (3) Patients are then required to stay for an observation period to monitor for adverse reactions or for clinician-guided adjunct psychotherapy, as conjunctive therapy has been reported to significantly amplify long-term cognitive-behavioral benefits associated with ketamine therapies. (4)

Because of ketamine’s classification as a Schedule III drug, state and federal statutes regulate prescribers and their clinics. (5) Important safeguards include required in-person treatment and medical supervision. However, in 2020 these provisions were no longer mandated, after the federal public health emergency declaration (PHED) waived in-person health encounter requirements for controlled substance prescriptions. (6) Consequently, in-clinic ketamine infusions monitored by trained healthcare professionals were transformed into at-home, “use-at-your-own-risk” treatments. As a result, questionable telehealth practices usurped in-clinic ketamine regulations, generating legal and medical concerns.

Since the meteoric rise of in-person ketamine clinics, there has been a nationwide shortage of manufactured formulations. Mass-produced manufactured drugs are created under strict guidelines. The paucity of manufactured ketamine has encouraged telehealth providers to turn to compounding pharmacies. These pharmacies create customized medication dosages for specific individuals, and are therefore exempt from some FDA regulations. There has been minimal research on compounded ketamine formulations. (7) Most ketamine compounded formulations consist of oral tablets, lozenges, or nasal sprays. (8) *The Washington Post* describes how telehealth practitioner Dr. Scott Smith garnered thousands of online patients via the website Reddit, ordered generic lozenges from online compounding pharmacies, and distributed them to patients across the country for several years, until the Drug Enforcement Administration suspended his controlled substance license. Medical experts warn against online oral ketamine prescribers like Dr. Smith, claiming these practitioners provide patients with inadequate drug-safety information. (10) The FDA shares this concern and recommends only using such medications under the direct supervision of a clinician. There are no FDA-approved oral or intranasal racemic ketamine preparations for any medical indication. In fact, the FDA has not approved specific racemic ketamine dosing for any psychiatric condition. (7)

Many telepsychiatry practices also expanded their scope across state lines, thanks to PHED-granted leniency for controlled substance prescribing. Prior to the pandemic, the Ryan Haight Act prohibited out-of-state controlled substance prescriptions. (6) After the

PHED, any practitioner with a DEA license could prescribe scheduled drugs in virtually any state. Dr. Smith even boasted state controlled substance licenses from 45 states. (10) Moreover, a DEA license allows practitioners to directly ship prescriptions or medications. Telehealth platforms adapted this logic to extend their business to any paying customer, referencing the Code of Federal Regulations on Controlled Substances, which states “an individual practitioner may administer or dispense directly a controlled substance listed in Schedule III, IV, or V in the course of his/her professional practice without a prescription...” (11) In doing so, practitioners bypassed prescriptions and local pharmacies altogether, maximizing telehealth company profits. Companies began partnering with physicians to order compounded ketamine *en masse* and distribute the drug to patients across the nation.

With regard to medical implications, unsupervised ketamine administration increases the risk of overdose. Though death from ketamine toxicity is relatively rare, overdosing still has negative effects, including paranoia, hallucinations, and anxiety. On the other hand, underdosing can result in treatment non-response. (11) According to the FDA, anaphylaxis, increased suicidal ideation, hypertensive crisis, and respiratory depression can also occur, especially with unregulated oral and intranasal compounded ketamine. The consequences can be fatal without direct observation and immediate access to care. For example, in April 2023, the FDA reported that an individual who was prescribed oral ketamine for PTSD experienced significant respiratory depression after taking an unsupervised dose. Toxicology revealed that the patient’s ketamine blood level was twice that of anesthesia levels. (7) Another drawback of at-home ketamine treatment is that individuals with TRD or refractory suicidal ideation are unable to receive the full benefits of ketamine therapy without adjuvant psychotherapy, resulting in subtherapeutic treatment. Without combination therapy, patients may be more likely to rely solely on the drug to improve their functioning, promoting psychological dependence and abuse.

As pandemic pandemonium subsides, emergency statutes have expired, resulting in legal ramifications for telemedicine ketamine providers. The PHED was discontinued November 11, 2023, and clinicians can no longer prescribe controlled substances to new

patients without in-person consultations. However, established patients have a one-year extension to transition to in-person visits. (10) The expiration of the PHED will keep ketamine consults within state lines, but the expectations for subsequent appointments are still unclear. Legal ambiguity could continue to drive unfettered online ketamine prescribing, just as financial factors and drug shortages drive the use of compounded medications. Government response may eventually follow, resulting in new legislation as this industry's evolution unfolds.

References:

1. Duman RS, Li N, Liu RJ, Duric V, et al. Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology*. 2012 Jan;62(1):35-411
2. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. *Anesth Essays Res*. 2014;8:283-290
3. Parikh SV, Lopez D, Vande Voort JL, et al. Developing an IV Ketamine Clinic for Treatment-Resistant Depression: a Primer. *Psychopharmacol Bull*. 2021;51:109-124
4. Smith-Apeldoorn SY, Veraart JK, Spijker J, et al. Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability. *Lancet Psychiatry*. 2022;9:907-921
5. Abbassi C. Key Legal Considerations Relating to Ketamine Behavioral Health Platforms. *Health Care Law Brief Blog*. Available at <https://www.proskauer.com/blog/key-legal-considerations-relating-to-ketamine-behavioral-health-platforms>
6. Maheu M. Prescribing Controlled Substances Across State Lines — What to Expect After TeleHealth Waiver Expiration. *Telehealth.org*. Available at <https://telehealth.org/prescribing-controlled-substances-across-state-lines-what-to-expect-after-the-telehealth-waiver-expiration/>
7. U.S. Food & Drug Administration: FDA warns patients and health care providers about potential risks associated with compounded ketamine products, including oral formulations, for the treatment of psychiatric disorders. Available at

<https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine>

8. Jacobs A: FDA Issues Warning Over Misuse of Ketamine. Available at <https://www.nytimes.com/2023/10/11/health/fda-ketamine-warning.html>
9. Gilbert D: This doctor prescribes ketamine to thousands online. It's all legal. Available at <https://www.washingtonpost.com/business/2022/12/30/ketamine-telemedicine-covid-emergency/>
10. Putka S: DEA Shuts Down Telehealth Ketamine Prescriber. Available at <https://www.medpagetoday.com/special-reports/features/104467>
11. Drug Enforcement Administration: Department of Justice: 21 CFR Part 1306 - Controlled Substances Listed in Schedules III, IV, and V
12. Sleight J, Harvey M, Voss L, et al. Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care. 2014;4:76-81