Ketamine Treatment in Psychiatric Practice: An Evidence-Based Clinical Overview

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What Is Ketamine?

Ketamine was developed in the 1960s as an anesthetic and has been used as such in clinical medicine ever since. Its antidepressant properties were first reported in 2000 in a seminal paper by Berman et al, but it took almost another 10 years before academic and clinical interest began to pick up on it. Since then, its research and use has expanded exponentially, proving effective in treating severe depression, suicidal ideation, PTSD, and premenstrual mood symptoms, with emerging evidence for additional conditions.

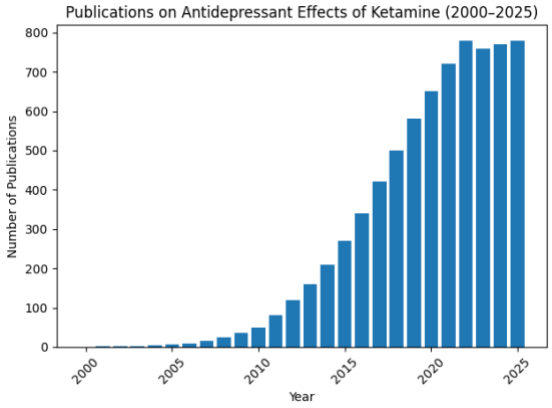

Figure 1 Growth in the number of publications on the antidepressant effect of ketamine between 2000 and 2025 (approximate numbers)

Ketamine stands apart from conventional antidepressants in three fundamental respects: the **speed** of its antidepressant effect (hours rather than weeks), its **mechanism of action** (acting on the glutamate system rather than the serotonin or norepinephrine systems), and its capacity to produce relief even in patients for whom multiple prior treatments have failed.

Strictly speaking, ketamine is a dissociative agent, not a psychedelic one, although it is frequently called that due to the striking similarities between the subjective experiences they create in those who use them. It is also not a sedative**.** Sedatives work by activating GABA-A receptors, producing a general calming effect on the central nervous system. This is how Valium, Xanax, Ambien, and alcohol all work. Ketamine works differently, instead inhibiting portions of the GABA system via an indirect route, rather than activating

it. The neurological effect is not sedation, but a state called *dissociative anesthesia* in which conscious awareness is decoupled from bodily sensation. A person under ketamine's influence may appear sedated but physiologically is not since ketamine typically **increases** blood pressure and heart rate rather than reducing it as a sedative might. This distinction matters enormously for clinical safety. The 2019 death of Elijah McClain, who was injected with ketamine by EMTs attempting to "sedate" him during an agitated police arrest, illustrates what can go wrong when ketamine is misused as a sedative in a stressful non-clinical environment, a context for which it is entirely unsuitable.

How Ketamine Works in the Brain

NMDA Receptor Antagonism

Ketamine acts primarily as an NMDA (N-methyl-D-aspartate) receptor antagonist. The NMDA receptor is a specialized excitatory receptor involved in synaptic plasticity, learning, and memory. When ketamine blocks the receptor, it triggers a cascade of downstream effects including a rapid increase in synaptic signaling through the AMPA receptor pathway, leading to the release of brain-derived neurotrophic factor (BDNF), and the formation of new neural connections (synaptogenesis). These processes, which conventional antidepressants achieve only slowly over weeks via the serotonin and norepinephrine systems, happen within hours with ketamine. A key reference is Zanos & Gould, 2018. Further scientific reading is available on the clinic's resources page.

Chemistry: Isomers, Metabolism, and the Entourage Effect

Ketamine exists as a racemic mixture of two mirror-image molecules (isomers), s-ketamine and r-ketamine. The s-isomer (esketamine) has a higher affinity for the NMDA receptor. R-ketamine has shown longer-lasting antidepressant effects in animal studies. Esketamine is FDA-approved as an adjunctive treatment for treatment-resistant depression and acute suicidal ideation in the form of the nasal spray Spravato. Ketamine infusions and intramuscular injections use the original racemic mixture.

Ketamine is metabolized in the liver, creating multiple breakdown products, some of which are themselves psychoactive. Notably, (2R,6R)-hydroxynorketamine (HNK) has shown therapeutic potential in preclinical studies while being devoid of dissociative properties and abuse potential. The total clinical effect of ketamine is therefore the sum of the parent compound plus its metabolites, which is referred to as an "entourage effect." Thus, the route of administration matters, since approximately 80% of oral ketamine is metabolized

before reaching the brain, whereas injected forms reach the brain before encountering metabolism by the liver. More detail on routes of administration is available here.

The Opioid Connection

An increasingly recognized dimension of ketamine's pharmacology involves its interaction with the opioid system. A small but influential Stanford trial tested ketamine on patients with treatment-resistant depression. Before the ketamine was administered, patients had received either a placebo or naltrexone (an opioid blocker). When patients took naltrexone first, the rapid mood elevation that ketamine typically produces largely disappeared, even though the dissociative sensations still occurred. This finding suggests that the opioid system is specifically tied to ketamine's mood benefits, not to its psychedelic effects. A follow-up analysis found that naltrexone also blunted ketamine's antisuicidal effects.

The clinical implication is significant in that patients taking naltrexone for alcohol or opioid use disorder should discuss timing and coordination with their prescribing team before beginning ketamine treatment.

Effects on Specific Brain Structures

Ketamine acts on several key brain regions simultaneously. In the **prefrontal cortex,** it increases glutamate release, counteracting the synaptic atrophy associated with depression and promoting growth of new dendritic connections. In the **hippocampus,** it promotes long-term potentiation, strengthening the neural connections essential for learning and memory. In the **amygdala,** it reduces the hyperactivity associated with PTSD, improving hypervigilance and startle response.

A particularly important target is the lateral habenula (LHb), a small structure deep in the brain that functions as part of the brain's anti-reward system, activated by negative experiences such as failure, punishment, pain, and stress. In chronic depression, the LHb shows characteristic "burst firing" that causes motor suppression in brainstem nuclei, which plays a role in creating the emotions of apathy, anhedonia, and negativism. Ketamine inhibits this burst firing within minutes of administration. Professor Hailan Hu of Zhejiang University presented this research at the 2024 Oxford International Ketamine Conference.

At the network level, ketamine normalizes hyperconnectivity within the **Default Mode Network** in depressed patients, without changing connectivity in healthy individuals. It also increases activity of the **Salience Network**, restoring the balance between

introspective and externally focused processing. This network-level effect reverses after only a single treatment, which is why a minimum series of sessions is required.

Who Benefits from Ketamine Treatment?

Primary Indications

The strongest evidence for ketamine as an effective treatment is for **depression, suicidal ideation,** and **PTSD.**

Treatment-resistant depression is characterized by inadequate response to standard antidepressant therapies. The landmark STAR*D study found that a significant percentage of individuals do not respond to traditional antidepressants even after several attempts with adequate dosing and duration. Traditional antidepressants lead to full remission in approximately 30 to 40% of patients following one treatment cycle. Ketamine shows a significantly higher remission rate of 50 to 75%, with effects appearing in days rather than weeks (Murrough et al., 2013).

Ketamine's position in the management of suicidal ideation is particularly distinctive. Only three medications have been proven to have specific anti-suicidal effects: clozapine (an antipsychotic), lithium (a mood stabilizer), and ketamine. None of the three are traditional antidepressants, and there is no single known mechanism that explains their shared efficacy. Critically, suicidal ideation can improve remarkably **even when depression does not respond fully** to ketamine, which has significant clinical implications for high-risk patients. It is also worth noting that antidepressants have been conclusively proven to reduce suicidality only in patients over 65, are not proven in the 25 to 65 age group and are known to **increase** the risk of suicidal ideation in the 15 to 25 age group. More information is available at the Zero Suicide Institute.

Emerging Indications

Secondary indications include anxiety disorders, OCD, eating disorders, and substance use disorders, though the evidence base is less established. Pure anxiety disorders are less reliably responsive to ketamine than depression or PTSD.

An exciting area of emerging research is ketamine for postpartum depression. A randomized, placebo-controlled, double-blind trial published in *The British Medical Journal* found that a single low dose of esketamine (0.2 mg/kg intravenously) administered within 40 minutes of childbirth reduced the incidence of postpartum depression at day 42 from

25% in the placebo group to just 6.7% in the esketamine group — roughly a three-quarter reduction. Side effects, including temporary dizziness and mild hallucinations in approximately 45% of the treated group, were short-lived and resolved within 24 hours. While this treatment requires hospital-level administration, pregnant patients with a history of depression should discuss it with their care team before delivery.

What Ketamine Does Not Treat Well: Chronic Pain

A large Cochrane review combining data from 67 randomized controlled trials involving more than 2,300 participants found no clear evidence that typical subanesthetic dose ketamine reduces pain intensity over the short, medium, or longer term in chronic non-cancer pain conditions such as fibromyalgia, nerve pain, and complex regional pain syndrome (CRPS). The overall quality of evidence was rated "low to very low."

Very high-dose ketamine infusions (defined as doses approaching or reaching anesthetic levels) administered for several days continuously have been reported for severe, refractory chronic pain conditions, particularly complex regional pain syndrome (CRPS), but require intensive care unit monitoring with intubation or other aspiration precautions. The evidence base for these extreme doses is limited to case reports and small series rather than randomized controlled trials.

Point Loma Clinic does not administer ketamine for chronic pain, and we encourage individuals exploring this option to review the scientific literature carefully before proceeding with any ketamine-based pain clinic.

Contraindications

Ketamine is not appropriate for everyone. A full assessment of contraindications is part of every intake evaluation. Contraindications include:

- Unstable heart disease or uncontrolled high blood pressure
- Unstable epilepsy
- Psychosis
- Glaucoma
- Severe liver disease
- Current uncontrolled substance abuse
- Pregnancy (unknown effect on the fetus)
- Children (no data available)

- Active mania or hypomania. Bipolar disorder requires careful evaluation; rapid cycling and active mania are contraindications; severe bipolar depression may be treated with appropriate clinical oversight

What Ketamine Treatment Looks Like

Evaluation and Intake

Before beginning ketamine treatment at Point Loma Clinic, every patient completes a comprehensive psychiatric evaluation with Dr. Papp. This encompasses a thorough review of current complaints, the history of those complaints, relevant medical and life history, and laboratory tests if indicated. A full assessment is completed even for patients referred specifically for ketamine by other providers. Diagnostic clarity and clinical appropriateness are prerequisites, not afterthoughts.

Preparing for Treatment

A ketamine preparation session with Dr. Myers is scheduled before the first ketamine session for patients new to ketamine to educate them about the ketamine process and about ways to achieve the most from treatment. The clinic's patient preparation guide emphasizes the concepts of "set" (the mental state a patient brings to the experience) and "setting" (the physical and social environment), both of which can influence outcome.

Key preparation guidance includes:

- Minimize alcohol and recreational drugs before and after treatment; none the day of treatment
- Avoid eating for 4 hours before treatment (small amounts of clear liquids are OK)
- Take prescribed medication as directed by Dr. Papp; some medications should not be taken the day of treatment, either for safety reasons or because it reduces the effect of the ketamine
- Arrange a conflict-free ride after treatment; patients should not drive for at least six hours after treatment.
- Clear the day of stressors and interpersonal conflict, since studies have shown that stress can reduce the ketamine effectiveness.

The Treatment Course

The antidepressant effect of a single treatment typically lasts 6 hours to 10 to 14 days, rarely up to 30 days. Maintaining benefit requires the continuation of sessions at intervals determined by individual response.

The recommended initial course is six sessions administered over three weeks but this can be modified should scheduling problems arise. About one quarter of patients experience marked improvement within 48 hours of the first treatment; another half improve by the fifth or sixth visit; and the remaining quarter receive little or no benefit. If no improvement is seen after six treatments, additional sessions are not recommended. Patients pay session by session and may discontinue at any time, unlike some providers that require prepayment of six or more sessions.

After the initial series, session frequency tapers progressively to weekly, then biweekly, monthly, bimonthly, and eventually every two to three months or as needed. A few patients may need a more frequent scheduling to maintain improvement.

Administration Method

We use intramuscular (IM) ketamine exclusively, citing its reliability, simplicity, and strong safety profile. IM administration achieves 95 to 97% bioavailability. The clinic does not prescribe oral ketamine for home use due to safety concerns. Each session is personally administered and continuously monitored by Dr. Papp, with secure video monitoring as an additional safety measure. Only one patient is scheduled at a time and are given exclusive attention by Dr. Papp to maximize patient safety. Sessions last approximately two hours; the medication effects themselves typically last 40 to 70 minutes, followed by a structured discussion.

Monitoring the Effect

Informal assessment occurs at the start of each subsequent session when the treating clinician reviews the patient's experience since the prior treatment. Immediately following emergence from the dissociative state, patients are asked about their subjective experience during the session, overall mental state, and any adverse effects experienced.

Formal assessment is conducted at Point Loma Clinic using two validated questionnaires.

The Beck Depression Inventory (BDI) is a widely used self-report measure that asks patients to rate the severity of symptoms — such as sadness, guilt, sleep disturbance, and loss of interest — over the preceding two weeks. Each response is scored and summed to

produce an overall index of depressive symptom severity. Patients complete the BDI before their initial ketamine session and again after the sixth session, or whenever a two-week interval between treatments permits. This yields a numerical estimate of improvement, allowing us to characterize the severity of depression at baseline and track changes over the course of treatment.

The Profile of Mood States (POMS) is a self-report instrument that asks patients to rate how strongly they have been experiencing various emotions at the time of completion. Responses are organized into subscales representing dimensions such as tension, depression, anger, fatigue, and vigor, and are combined into a total score reflecting overall mood disturbance. Patients complete the POMS immediately before and after each ketamine session to gauge and document the acute effect of each treatment.

Following each ketamine visit, patients also complete a brief questionnaire addressing the general pleasantness and intensity of the experience, the presence or absence of out-of-body or perceptual phenomena, and any side effects. This information helps guide dosing decisions for subsequent sessions and informs any need to adjust medications to optimize the subjective experience.

Patients are additionally given the opportunity to write a narrative account of their experiences. Some of these accounts are referenced elsewhere in this article and in our blog posts.

All data collected is maintained exclusively within each patient's individual medical record and is kept strictly confidential.

Integrating Psychotherapy with Ketamine

Ketamine promotes neuroplasticity and increases connectivity across key brain networks, creating a window — particularly in the 24 to 48 hours after administration — during which new insights and shifts in perspective may be more accessible. Psychotherapy timed to this window helps consolidate neurobiological gains and translate them into lasting behavioral change. Point Loma Clinic refers to this approach as Ketamine Coordinated Therapy.

There are four levels of integration: ketamine alone; ketamine with psychotherapy not timed to the administration; ketamine with psychotherapy scheduled in the neuroplasticity window (the day after), and ketamine with psychotherapy conducted during the session itself. Each level offers different benefits, and the appropriate approach depends on the patient's presentation, history, and goals.

Psychotherapy During the Session

The most direct form of integration involves psychotherapy conducted while the patient is actively under ketamine's effects. Consider the case of Carla, a 48-year-old businesswoman who had experienced anxiety and panic attacks since age 16. Standard Cognitive Behavioral Therapy had been ineffective due to her rigid thinking and avoidance of certain topics. After beginning ketamine, which softened her cognitive rigidity and made her more open to new perspectives, a significant breakthrough occurred during a session in which psychotherapy was conducted while she was under the drug's effects. She began to talk about her traumatic childhood, which she had previously insisted was "wonderful," and gained insight into the origins of her anxiety and hypervigilance. Her improvement accelerated markedly after that session.

Higher-dose ketamine may specifically facilitate this kind of therapeutic work. Research suggests that ketamine's psychedelic properties can increase rapport, reduce defensiveness, and evoke transpersonal experiences that support transformation and decision-making.

Psychotherapy Timed After Ketamine Treatment

Psychotherapy coordinated to occur within 24-48 hours is the most common way that Point Loma Clinic adds psychotherapy. This can be done either with Dr. Myers or with a therapist outside our clinic.

The theoretical rationale for scheduling psychotherapy within 24 to 48 hours after ketamine is based on the concept of a **neuroplasticity window** that ketamine opens. During this period, several neurobiological changes occur that theoretically could enhance psychotherapeutic work:

Peak neuroplasticity: Neurophysiological changes emerge within 3-8 hours, consolidate by 24 hours, and are rarely detected beyond 3 days post-ketamine. These changes include rapid increases in glutamate release, AMPA receptor activation, BDNF signaling, and mTOR-mediated synaptogenesis, particularly in prefrontal cortical regions.

Mental flexibility window: The predictive processing theory suggests that ketamine creates a period of reduced rigid thinking patterns and increased cognitive flexibility that could facilitate psychotherapeutic insights and behavioral change.

Psychotherapy provided before, during, and following ketamine sessions is commonly practiced in ketamine-assisted psychotherapy protocols. However, there is tremendous variance in how this is applied, with no standardized timing protocols (for example in Veraart et al, 2026.)

The literature does not provide specific evidence-based guidance on whether psychotherapy should occur at 24 hours versus 48 hours versus other timeframes. The 24–48-hour window is based primarily on a **neurobiological theory** rather than clinical trial data demonstrating superiority of this specific timing.

Psychotherapy Timed Independent of the Ketamine Treatment

Sometimes, it just isn't practical to time the therapy specifically, especially if a patient is seeing a therapist outside the clinical coordination. Although therapy is usually beneficial to support the patients experiences and process material that may arise, it is best if the therapist understands both the process of the ketamine treatment and how the therapy might affect the ketamine itself, especially within the first 24 to 48 hours of administration.

No Psychotherapy with the Ketamine Treatment

For some patients, either because they have had ketamine in the past and don't believe that therapy would be beneficial, or for those patients who really do not want therapy, ketamine alone is appropriate. Although studies show that therapy added to the ketamine treatment can be beneficial, ketamine's therapeutic effects are robust enough for it to still be helpful when administered alone.

The Psychedelic Experience: What Patients Report

Point Loma Clinic collects narrative accounts of patients' experiences at the end of each session. These experiences vary enormously. Two patients, whose accounts are described in the Ketamine Dreams 1, developed persistent themes across sessions: one consistently experienced sandstone sculptures and shifting sand imagery in deep reds and purples; the other traveled through stars and constellations, reporting an overwhelming sense of beauty, calm, and hope. A third patient, whose narratives are documented in Ketamine Dreams 2 , described experiences ranging from hearing her own compositions in her mind's ear, to vivid architectural imagery rooted in personal memory, to a final session in which she found herself imagining the sunlit turrets of a castle in the Mediterranean. She heard songs she had not heard in decades, remembered a beloved relative, thought of her times with her boyfriend and she felt at ease and contented.

One patient, describing her seventh treatment, said: *"My chair, particularly the head rest, began to feel like my mother's chest. The sounds of the waves sounded more and more like the sounds of the passing cars outside my childhood bedroom window. I felt like I was home again with her, being held."* She went on to remember something about her mother's passing that helped her understand certain patterns in her own behavior. Experiences like these, when they occur, can be powerful therapeutic material.

When the Trip Is a Non-Event

Importantly, the psychedelic experience is **not necessary** for ketamine to be therapeutically effective. Some patients who have had intense sessions on prior visits occasionally have sessions in which nothing subjectively unusual occurs, what some patients call a "dud." Despite this, standard mood scales show their typical level of improvement, and clinical benefit follows in the days after. The neurobiological effects of ketamine operate independently of the subjective experience.

Predicting and Understanding Treatment Outcomes

Who Is Likely to Respond?

Predictors of non-response to ketamine for treatment-resistance are limited and inconsistent, with the largest patient-level meta-analysis finding no clinically actionable demographic or clinical features that reliably identify non-responders (Price et al, 2022). A few clinical, psychiatric, and biological factors have emerged as potential negative predictors across smaller studies, such as older age at disease onset, melancholic type depression, benzodiazepine use, comorbid metabolic syndrome, or comorbid borderline personality disorder.

Predictors of good response to ketamine for TRD remain similarly limited and inconsistent. A systematic review (Constantino, L, 2025) found some support for positive associations with anhedonia, sleep disturbances, and childhood physical abuse. The absence of psychiatric comorbidities is also favorable, as patients without comorbidities showed the greatest improvement. The same study also found the personality trait of openness to be associated with better response.

The Qualitative Difference from Antidepressants

Beyond response rates, the qualitative experience of improvement with ketamine is often strikingly different from that with conventional antidepressants. One patient described traditional antidepressants as requiring constant adjustment, "like shielding my eyes from the sun with my hand." Ketamine, by contrast, felt "like sitting under a wide umbrella" — allowing full relaxation without constant effort. Another patient found antidepressants like "wading through mud," while ketamine felt like "walking in gentle rain — any mud simply washes away." The common theme is the effortlessness of maintaining an improved mood with ketamine compared to conventional treatment.

The Importance of Psychiatric Context

One of the strongest arguments for administering ketamine within a comprehensive psychiatric practice is the capacity for real-time clinical recalibration. Consider Joe, a mid-fifties attorney with a long history of treatment-resistant depression treated with ketamine over several years. Partial improvement allowed him to become more functional in business and develop a romantic relationship. Over time, however, he began reporting irritability, eventually losing a significant client due to outbursts at work. Sleep difficulties emerged. As these symptoms progressed and his antidepressant was tapered, it became clear that Joe had become hypomanic. Ketamine was appropriately discontinued, and his diagnosis was revised from 'Chronic Depression, questionable bipolar disorder' to 'bipolar disorder.' This case is also discussed in detail in the navigating bipolar and ketamine post.

Had Joe been receiving ketamine at a standalone ketamine clinic while seeing a general psychiatrist only every three to six months, this shift might have gone undetected across many sessions. When ketamine administration and ongoing psychiatric management occur within the same practice, clinical recalibration can happen as soon as something changes.

Safety, Risks, and the Case Against At-Home Ketamine

Side Effects During Treatment

Side effects during a ketamine session are generally manageable and transient. Elevated blood pressure and heart rate occur in more than 80% of patients but are almost never clinically serious and may be addressed with premedication when indicated. Nausea and vertigo occur in 20 to 30% of patients and can be managed with anti-nausea medication. Anxiety during the session occurs in a similar proportion and typically responds to

reassurance or simple presence; antianxiety premedication is rarely needed. After the ketamine wears off, patients may experience temporary wooziness or headache.

Long-Term Safety

Long-term side effects are not well characterized due to limited systematic data. The risk of triggering addiction is believed to be very low. Some concerns about liver function exist but are thought to be clinically insignificant at therapeutic doses. Severe urinary cystitis is documented in heavy recreational abusers of ketamine, but not in patients receiving therapeutic doses under medical supervision.

The Growth of Ketamine Clinics

Since roughly 2010 and accelerating sharply after the mid-2010s, ketamine has moved from a largely experimental intervention into a rapidly expanding commercial landscape. By some estimates, the number of clinics in the United States offering ketamine grew from fewer than one hundred around 2015 to well over 1,500 by 2024, accompanied by a multibillion-dollar market and sustained annual growth.

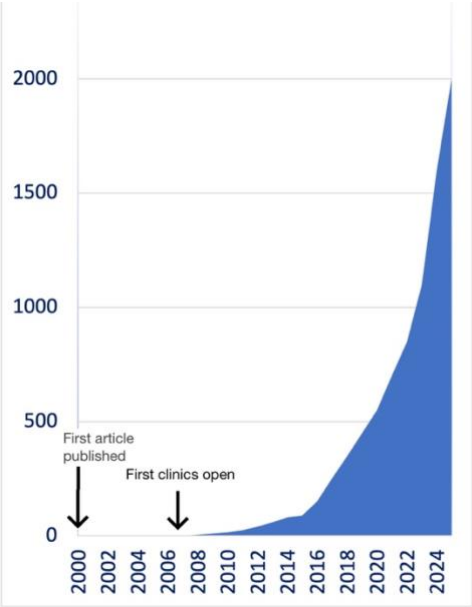

Figure 2 The growth of ketamine clinics in the US since 2000

This growth has unfolded largely in advance of clear regulatory frameworks or consensus standards. Ketamine's use for most psychiatric indications is predominantly off-label, allowing a wide range of providers to enter the field. As a result, alongside academically affiliated or carefully supervised practices, there has been a marked proliferation of loosely structured, consumer-facing "ketamine clinics," often staffed by non-psychiatrists or midlevel providers, and in some cases extending into telemedicine models with minimal direct oversight.

Within this landscape, concerns have increasingly centered on the emergence of high-volume, revenue-driven facilities in which clinical rigor appears secondary to throughput. Reports describe clinics relying on cursory screening tools, limited coordination with patients' existing mental health providers, and protocols that diverge substantially from those studied in controlled trials. In some settings, patients may receive ketamine for

unsupervised at-home use, while the broader therapeutic context, such as psychotherapy, longitudinal follow-up, diagnostic clarity, remains thin or absent.

The Dangers of At-Home Ketamine

The growth of take-home ketamine prescriptions delivered as nasal sprays or oral lozenges (troches), sometimes without any direct outside support, raises serious concerns. At-home ketamine lacks the safeguards of clinical administration. Ketamine is a Schedule III controlled substance due to its potential for abuse and dependency. Its dissociative effects may be sought recreationally, particularly by individuals with a history of substance use disorders (Morgan & Curran, 2012). Without clinical monitoring, side effects including dissociation, confusion, and blood pressure elevation cannot be immediately addressed (Andrade, 2017). Dosing errors, both under- and over-dosing, are more likely, and the long-term safety of unsupervised chronic ketamine use remains poorly understood (Memon et al., 2020). Because of these risks, we do not prescribe take-home ketamine.

The Matthew Perry Case

The dangers of unmonitored ketamine use were brought to public attention by the death of actor Matthew Perry. The autopsy revealed high levels of ketamine in his system, with the likely cause of death involving cardiovascular overstimulation, respiratory depression, and drowning; ketamine's compounded the effects on an already compromised coronary arteries. Therapeutic levels of buprenorphine and lorazepam, both of which depress respiration, were also present. The presence of ketamine in his stomach indicated oral consumption, which would have occurred outside a clinical setting.

Under proper medical supervision, ketamine treatments have not been known to result in fatalities. A study of 758 cases of ketamine poisoning found a mortality rate of only 1.2% (Palamar et al.), and in that data the fatalities were associated with misuse rather than supervised clinical use. In April 2023, the FDA received an adverse event report of a patient who experienced respiratory depression after taking compounded oral ketamine outside a healthcare setting, with blood levels approximately twice those used in anesthesia — an event that foreshadowed the Perry case. Adverse events can be reported to the FDA's MedWatch program.

Ketamine in the Broader Landscape of Psychiatric Treatment

Treatment-Resistant Depression: A Systemic Problem

Treatment-resistant depression (TRD) does not always mean that depression is truly refractory. The STAR*D study and subsequent research suggest that prior treatments are frequently inadequate in dosage or duration, therefore before a label of “treatment resistant” is applied to depression, it should be considered that it may have simply been “poorly treated”. Perhaps a better conceptualization would be call it “difficult-to-treat depression.” Underlying physical conditions such as thyroid disorders, chronic pain, co-occurring anxiety or OCD can also complicate depression and should be addressed before or alongside antidepressant treatment. Pharmacogenomic testing, which identifies genetic markers affecting how a patient metabolizes medications, can substantially shorten the trial-and-error process by guiding medication selection and dosing (Porcelli et al., 2011). Point Loma Clinic integrates pharmacogenomic testing as part of its precision psychiatry approach.

The Psychedelic Renaissance

Ketamine's emergence as a psychiatric treatment coincides with a broader renaissance in psychedelic psychiatry. Large clinical trials are now studying psilocybin, MDMA, and LSD for depression, PTSD, anxiety, and substance use disorders. Several have received Breakthrough Therapy designation from the FDA. Ketamine is classified as a nonclassical psychedelic and is currently the only agent in this category with established use in routine psychiatric practice.

Classical psychedelics such as psilocybin, LSD, DMT, and mescaline can induce profound altered states including ego-dissolution and synesthesia. Their therapeutic indices are notably broad. However, even at normal doses they can produce anxiety, confusion, and physiological stress, and rare serious adverse events such as suicidality, mania, and prolonged dissociation are documented, particularly in individuals with preexisting psychiatric conditions. MDMA presents a more complex risk profile, with more frequent adverse effects and documented cases of severe outcomes with heavy use. The promise of these agents is real, but so is the need for rigorous clinical oversight.

The 2024 Oxford International Ketamine Conference

The Oxford Ketamine International Conference in March 2024 brought together leading researchers and clinicians from around the world. Dr. Papp attended and presented

research co-authored with Douglas Myers-Turnbull: *"Tracking the Effect of Repeated Use of Ketamine for Depression in a Private Practice Setting."* The conference featured talks by Dr. Rupert McShane, a consultant psychiatrist at Oxford Health NHS Foundation Trust and a leading advocate for ketamine in severe depression, and Professor David Nutt, whose book Psychedelics: The Revolutionary Drugs That Could Change Your Life is recommended by the clinic. Drs. Papp and Myers also give annual lectures on ketamine to Alliant University as part of their Speaker Series.

About the Authors

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Dr. Papp is a board-certified psychiatrist specializing in adult psychopharmacology and interventional treatments, with a focus on treatment-resistant mood disorders. He directed the ketamine program in the Department of Psychiatry at UCSD before continuing this work at Point Loma Clinic, where he has administered ketamine since 2017. He is currently an Assistant Clinical Professor at UCSD in Family Medicine and an Adjunct Professor at Alliant University. He published the first two peer-reviewed articles on antidepressant discontinuation syndrome ("brain zaps"). He has given yearly webinars on ketamine at Alliant University and presented at the Oxford International Ketamine Conferences. Full biography: pointlomaclinic.com/alexander-papp

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Dr. Myers is a licensed psychologist and clinical psychopharmacologist. She holds a postdoctoral Master's in Clinical Psychopharmacology in addition to her doctorate in psychology, enabling substantive coordination of both psychological and pharmacological dimensions of ketamine treatment. She teaches psychopharmacology as an Adjunct Professor in the MSCP program at Alliant University. She co-authored a book chapter on traumatic grief with Donald Meichenbaum, PhD and has given yearly webinars on ketamine at Alliant University. Full biography: pointlomaclinic.com/julie-myers

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FDA MedWatch Adverse Event Reporting Program

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