

SCIENCE

# Psychedelic Medicine 101: The curious case of ketamine

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Vials of Ketamine  
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A psychedelic renaissance is underway in medical research as certain taboo drugs return to the hands of doctors and researchers after decades in the wilderness. Once considered illicit, with no medical value, these psychedelic compounds are now being legitimately evaluated by scientists and revolutionizing how we practice medicine.

Psychedelic medicine 101 is a series that will investigate the past, present and future medical uses of these formerly taboo substances. Our first feature examined the story of [psilocybin and magic mushrooms](#), while this new episode documents the curious story of ketamine, initially developed to be an anesthetic before researchers and psychonauts discovered its unique and unusual effects on the brain.



*Intravenous administration has shown to be one of the most common clinical ways to deliver the drug*

## The curious case of ketamine

In 1956, a chemist at pharmaceutical company Parke Davis in Detroit, Michigan was experimenting with synthesizing new compounds in an attempt to find a better anesthetic. A compound called phencyclidine was initially created, and in early animal studies it demonstrated defiantly unusual effects. Some animals exhibited a drunk-like state when administered with it, while others entered states of delirium.

Human tests quickly ruled out the compound as clinically useful with some patients exhibiting major delirious and dissociative states for prolonged periods of time. This was despite the fact the it did seem to function remarkably well as an anesthetic. In later years, phencyclidine hit the streets as a recreational drug, becoming infamous due it its violent side effects. Its street name was PCP, or angel dust.

In the early 1960s, Parke Davis researchers began searching for a phencyclidine derivative that could limit the compounds unmanageable side effects. It was here that ketamine was born and after successful animal tests it was administered to the first human subject in 1964, demonstrating remarkable anesthetic effects.

Initially approved for veterinary uses, ketamine quickly found a place as an effective short-acting anesthetic, officially passed by the FDA in 1970 for human uses. One of its first major human uses was as a battlefield anesthetic in Vietnam. It has been suggested that this initial use in the early 1970s was what led to it moving into recreational circles as veterans returned to the United States and continued using the drug.

Non-medical uses continued throughout the 1970s, culminating in several high profile publications "outing" the drug. Perhaps the most infamous of these accounts came in scientist and psychonaut John C. Lilly's 1978 autobiography *The Scientist: A Novel Autobiography*.



*John Lilly and his infamous isolation tank*

[WikiCommons](#)

## **Ketamine, sensory deprivation and alien communication**

John C. Lilly is perhaps best known for his work blending LSD, isolation tanks and human-animal communications. After developing the first isolation tank in 1954, Lilly began experimenting with LSD in the tanks in the early 1960s. His extreme work sat at the boundary of conventional science, and the extraordinary 1980 psychedelic film *Altered States* was significantly inspired by his experiences.

It was the early 1970s, however, when Lilly first crossed paths with ketamine. Lilly had long suffered extreme migraines, almost daily, for much of his life. During an attack, a physician friend suggested ketamine may be helpful. So Lilly jumped into an isolation tank, was injected with a small dose of ketamine, and his migraine disappeared ... for 20 minutes. When it roared back his physician friend gave him another injection, this

time double the dose. For about half an hour the migraine disappeared, but then it stormed back, so finally the physician again doubled the dose and sent Lilly back into the tank.

After an hour Lilly got out of the tank and his migraine had gone. A month later, with his migraine still yet to return, Lilly became convinced ketamine had somehow reprogrammed his brain in ways that his earlier massive LSD experiences couldn't. For the next few years Lilly's personal ketamine experiments became more and more extreme.

Lilly became convinced he could communicate with a network of extraterrestrial entities he dubbed ECCO, or the Earth Coincidence Control Office. ECCO guided Lilly's research but as he began to consume more and more ketamine he came across another, more malevolent entity called SSI, Solid State Intelligence.

SSI was a massive cosmic supercomputer, with evil intent. At one point, in the midst of an epic nearly month-long physical experiment with ketamine, consisting of injections nearly every hour, Lilly tried to contact President Gerald Ford to warn the world of a potential doomsday scenario. One of the president's aides intervened before Lilly could reach Ford.

These stories, and others, recounted in the late 1970s, slowly added to the infamy surrounding ketamine, but they also started to pique the attention of the authorities. The peripheral clinical uses of the substance were still pervasive enough for it to not be completely regulated until the United States government moved to make it a Schedule III controlled drug in 1999. This added a degree of regulatory oversight as to how the drug was dispensed but still allowed it to be utilized for clinical purposes.



*William Hurt in Altered States, a film loosely based on the experiences of John Lilly*  
Warner Bros

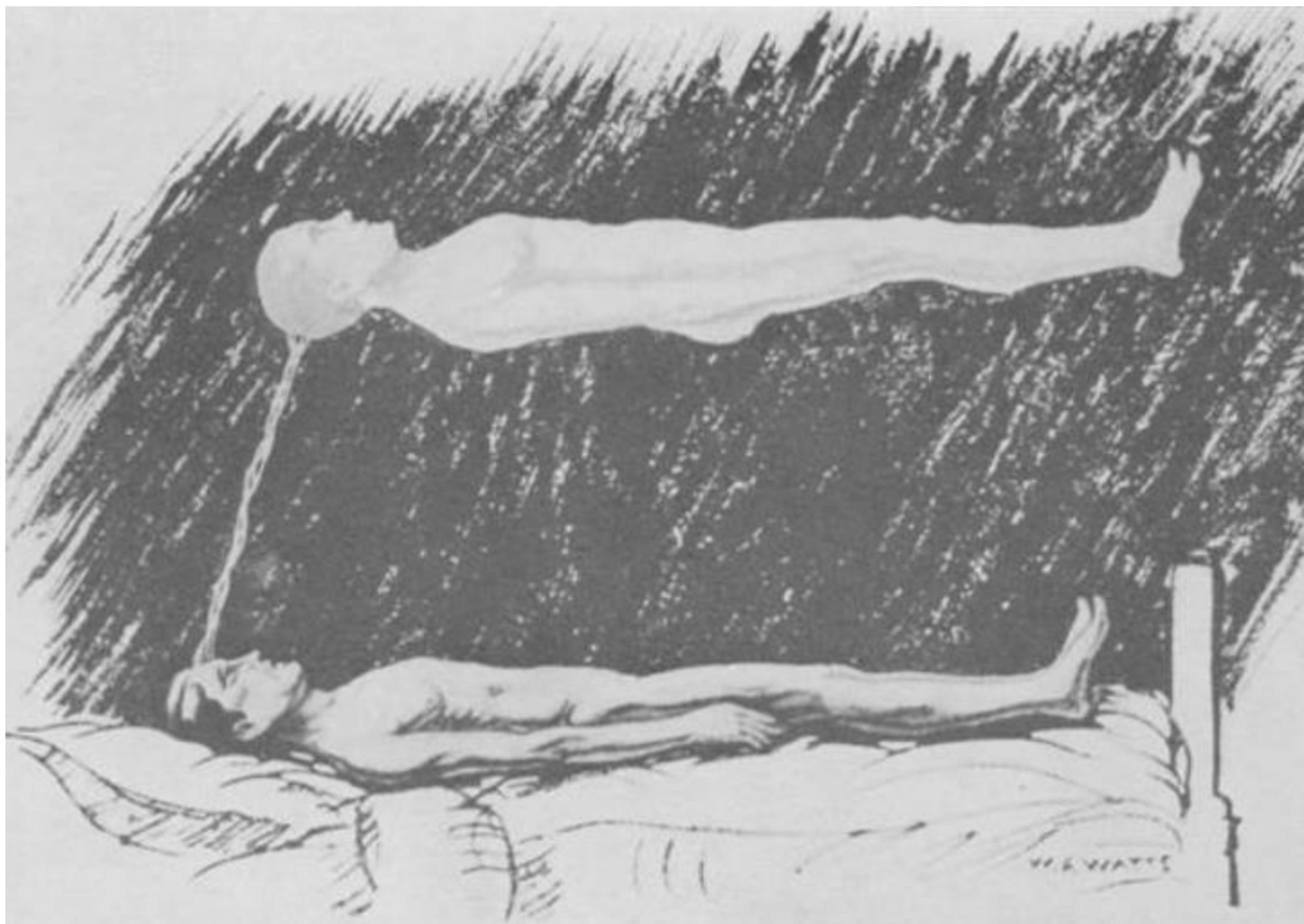
## The Russian research

In 1985, two Russian researchers hypothesized that ketamine could be a good drug to utilize in a psychotherapeutic context. It was short-acting, controllable, relatively accessible and known to induce psychedelic experiences. For the next decade, Evgeny Krupitsky and his team at the Leningrad Regional Center for Alcoholism and Drug Addiction Therapy pioneered what they called [Ketamine Psychedelic Therapy](#).

[Over the next decade](#), ketamine was used to treat more than 1,000 patients for an assortment of [drug dependencies](#), primarily alcoholism. In a systemic study of the work, published in 1997, the researchers reported that the KPT process they developed resulted in zero major side effects, such as protracted psychoses, flashbacks, agitation, or ketamine abuse. It also proved to be extremely effective in helping patients, with total abstinence rates for more than one year in KPT-treated alcoholic patients hitting around 65 percent compared to conventional treatment which was only successful in 24 percent of patients after one year.

For an extended period of time across the 1980s and early 1990s, this Russian team were extraordinarily the only researchers in the world investigating the therapeutic outcomes of ketamine. Krupitsky suggested this could be because Russia was not suffering from a culture of recreational psychedelic usage, which helped allow his work to continue for so long with no authoritative challenge.

"It seems to be an especially powerful tool in Russia, where there was no psychedelic revolution in the 1960's and almost nobody knows what "psychedelic" means or can even imagine that this drug can be used for recreation," the researchers concluded in their ten-year report.



*Ketamine is known for generating a profoundly dissociative out-of-body experience*

**WikiCommons**

## **The 21st century resurgence**

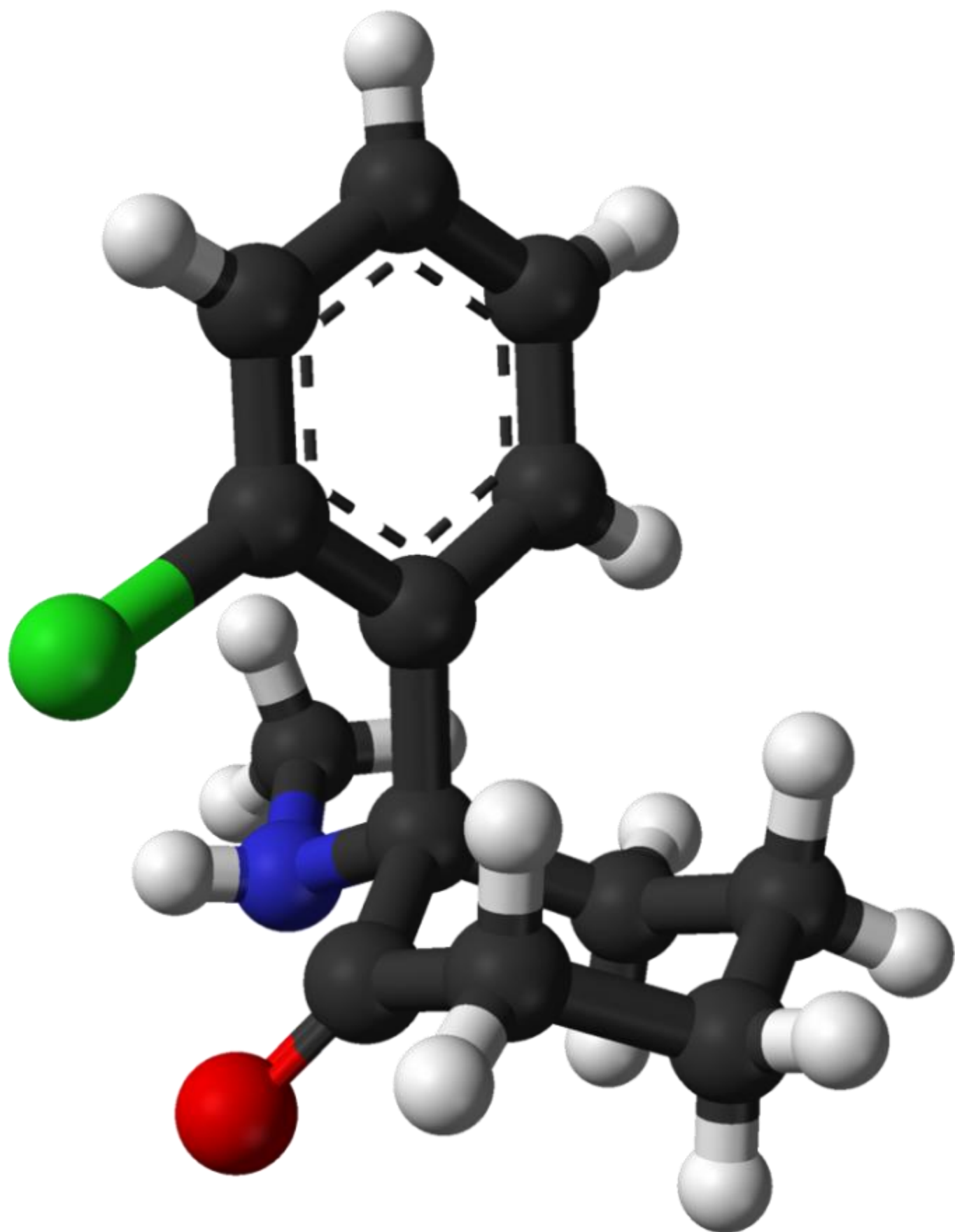
In the early 2000s, ketamine began to reemerge in Western research circles as a potential therapeutic agent, initially for depression. A [very small study](#) published in 2000 highlighted the drug's impressive antidepressant qualities, but it was a [2006 study](#) that really turned the tide.

The study, from the National Institute of Mental Health (NIMH), highlighted the remarkably rapid anti-depressant effects of ketamine. It was a small but strong piece of research involving a cohort of patients diagnosed with major, treatment-resistant depression. Two small doses of ketamine were administered, one week apart, and by the end of the first day 71 percent of subjects in the ketamine group reported a nearly 50 percent decline in their symptoms. Even more remarkable, after a week nearly a third of the ketamine group reported complete remission of their depressive symptoms.

This kind of rapid and immense effect was unheard of and the study [hit the mainstream media](#), propelling ketamine into the news for something other than an illicit street use for the first time in years.

The rapid anti-depressant effect of ketamine has been a fundamental and exciting area of research in recent years with scientists slowly homing in on the extraordinarily unique qualities of how the drug operates on the brain. [A 2017 study from Columbia University Medical Center](#) revealed impressive results when examining patients suffering from acute suicidal thoughts.

The study, composed of 80 patients with clinically significant suicidal thoughts, displayed a major reduction in reducing such thoughts within 24 hours of a single low-dose infusion. A six-week follow up also found the effects impressively held for an extended duration, especially when compared to a control-group that were administered a sedative called midazolam.



*A model of the ketamine molecule*

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## But how does it work?

How the drug actually works to achieve its rapid anti-depressant effects is a hot area of research. While it has been known for several decades that [ketamine blocks a protein](#) receptor in the brain called N-methyl-D-aspartate (NMDA), it hasn't been understood exactly where in the brain this mechanism could be operating.

[A recent study from Zhejiang University in China](#) excitingly revealed that this mechanism could be concentrated in the lateral habenula, an area of the brain often referred to as our "anti-reward center." Overactivity in the lateral habenula has been strongly related to depression and the new study revealed that ketamine directly reduces neuronal activity in that region.

Ketamine's broad use as a pain- and depression-relieving agent is finding burgeoning uses in treating other conditions peripherally connected to those symptoms. A growing body of anecdotal patient-driven evidence is suggesting the drug could be effective in treating fibromyalgia and chronic fatigue syndrome, two chronic conditions that are somewhat linked by widespread feelings of pain and fatigue.

In regards to fibromyalgia, some small studies have found ketamine to be incredibly effective in reducing acute pain related to the condition. The effects were frustratingly short-lived, unfortunately, but some patients have reported single infusions dulling pain for up to three weeks.

The use of ketamine to treat chronic fatigue syndrome is still in the nascent research stages, but [a 2016 study](#) revealed a fascinating insight into the drug as an anti-fatigue compound. While fatigue and depression are profoundly interlinked, the broader NMDA-blocking effects of ketamine are convincingly hypothesized to potentially improve the symptoms of patients suffering from chronic fatigue.

The 2016 study was small, and limited to patients being treated with ketamine for bipolar disorder during an episode of acute depression. It found that ketamine significantly improved symptoms of fatigue when compared to patients in the placebo group, with the anti-fatigue effects most prominent 48 hours after the initial infusion event. The study concludes by suggesting ketamine's NMDA receptor inhibition could be a novel target for anti-fatigue interventions in a variety of conditions, including chronic fatigue syndrome.



*The urban myth of ketamine as a horse tranquilizer became prominent as the drug moved into recreational circles in the 1980s and 1990s*

[Steven Lilley / Flickr](#) ([CC BY SA 2.0](#))

## **The rise of the ketamine clinic**

Unlike other more restricted drugs, ketamine is still available for medical uses. This has led to the recent upsurge of ketamine clinics in the United States. Ketamine is legally approved for use as an anesthetic, but its off-label use for other conditions is not illegal.

Since around 2015, it is estimated that well over 100 ketamine clinics have opened up in the US. These clinics target patients looking for an alternate way to treat their depression. For up to US\$1,000 a dose, patients can receive an infusion of ketamine either weekly or monthly. Different clinics have different treatment processes, from specific 10-week programs to more casual dose-by-dose appointments.

It's the wild west of medical treatments out there, with no clear science on how long these treatments last, or how safe long-term ketamine use like this actually is. The CEO of Actify Neurotherapies, a chain of 10 treatment centers, [said recently](#) "It scares the hell out of me that this is still unregulated."

Actify Neurotherapies is [actively resisting](#) the term "ketamine clinic," recently rebranding itself as a mental health clinic that happens to also provide off-label ketamine treatments. While Actify is positioning itself at the more credible end of the off-label ketamine provider spectrum, it is still part of a troubling, unregulated industry with the science yet to offer real clarity on the best way this drug should be delivered.



*Well over 100 ketamine clinics are operating in the United States*

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## **A little less psychedelic?**

The giant hurdle facing most ketamine research is trying to find a way to overcome the often unpleasant dissociative psychedelic effects of the drug. While NMDA-receptor antagonism is looking like an exciting new pathway to treat a whole host of conditions, the side effects of ketamine are proving tricky to manage when implemented into broader clinical applications.

[A recent Australian trial](#) into a ketamine nasal spray for treating depression had to be aborted after several participants started to experience psychotic-like side effects. One of the researchers suggested the dose problems stemmed from inconsistencies in the nasal-delivery method.

"We saw a range of tolerance levels and we think it's because one person's blood vessels in the nose can be so different to the next person's, and when you spray, it crosses the thin lining, gets taken into the blood and straight to the brain. Some people got huge hits."

Several researchers are now racing to develop compounds chemically similar to ketamine that still act on NMDA receptors but can reduce the psychoactive side effects. One of the most promising new alternatives is called [esketamine](#), and it is currently at the tail end of Phase III clinical trials.

Esketamine is an isomer of ketamine, and reportedly has slightly less dissociative characteristics compared to its sibling. It is thought to be twice as potent as ketamine, which means it is suggested that lower doses could have similar NMDA-inhibiting effects to ketamine without the equivalent hallucinogenic result.

Despite the FDA offering esketamine a [breakthrough designation in 2016](#), suggesting the compound is highly effective and will be rapidly pushed through the trial process, results have been decidedly mixed over the past few years. [Most recently](#), some of the early Phase III results suggest the compound is only mildly effective, and in some cases barely better than the placebo control.

## **Ketamine + therapy = success?**

Of course, some researchers are finding ways to work with the compound's extremely hallucinogenic properties. An exciting new trial currently underway at the University of

Exeter and University College London is directly inspired by Evgeny Krupitsky's 1980s research in Russia. The trial is called [KARE - Ketamine for reduction of Alcoholic Relapse](#), and it is setting out to examine how well ketamine, in conjunction with psychotherapy, can reduce alcohol dependence and promote abstinence.

The rigorous study, which is double blind and placebo-controlled, involves subjects being administered one dose of ketamine a week for a period of three weeks, alongside seven sessions of cognitive behavioral therapy. The study has a six-month follow-up phase to better understand the long-term effects of this kind of ketamine-assisted psychotherapeutic treatment.

Unlike the attempts to create a less psychoactive compound, this research suggests the holistic effect of ketamine could be vital to its absolute efficacy. The often unwanted hallucinogenic effects may very well be important. And unlike some of the ketamine clinics popping up around the US, this trial offers ketamine within the context of a controlled series of psychotherapy sessions helping patients integrate their experiences into positive outcomes.

The story of ketamine is a curious one, defiantly unlike other psychedelic substances being co-opted for medical uses. Ketamine is essentially legal, prescribable, yet still wholly experimental. It works on the brain in a completely novel way and we are only just understanding its broad potential uses.

With the rise of ketamine clinics, a strange kind of clinical practice has jumped ahead of research, giving rise to a wild west of drug providers administering the compound as a magic bullet for anything and everything in an unregulated landscape. More research undeniably needs to be done before we understand this deeply mysterious and unique drug, but it is looking like it will certainly become a fundamentally important compound in a bright future of psychedelic medicine.

## **We recommend**

1. [The Psychedelic Experience](#)  
William Wolf et al., *The Journal of Psychotherapy*, 2018
2. [What Lessons Can We Learn from This Patient's Journey with Migraine?](#)  
ReachMD
3. [The Next Chapter: MDMA-Assisted Psychotherapy for Chronic Treatment-Resistant PTSD](#)  
Aaron Wolfgang et al., *The American journal of psychiatry*, 2018
1. [Psychedelic Experiences in Acute Psychoses](#)  
Edwin L. Rabiner et al., *The Journal of Psychotherapy*, 2018
2. [Battling the Burden of Migraine. How Clinicians Can Help Patients](#)  
ReachMD
3. [What Tools Can We Use to Help Diagnose Migraine?](#)  
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