



Investigating the Current Ketamine Landscape in the United States

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Conflicts

I declare no conflicts of interest

Funding

National Institute on Drug Abuse:

- U01DA051126 (PI: Cottler)
- R01DA057289 (PI: Palamar)



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The Rapidly Shifting Ketamine Landscape in the US

JAMA Psychiatry

Wilkinson ST, Palamar J, Sanacora G. The Rapidly Shifting Ketamine Landscape in the United States. JAMA Psychiatry, 2023, in press.



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What is Ketamine?



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What is ketamine?

- Dissociative anesthetic
- Hallucinogen (not a psychedelic)
- It does not drastically reduce heart rate or breathing (unlike many other painkillers)
- Creates physical numbness without unconsciousness (and cataleptic effects)
- Schizophrenia-like symptoms, sometimes called an “emergence phenomenon”
- Similar effects from subanesthetic doses



Siegel RK. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. *NIDA Res Monogr.* 1978(21):119-147.
 Mion G. History of anaesthesia: The ketamine story - past, present and future. *Eur J Anaesthesiol.* 2017;34(9):571-575. Image: Reddit. "My cat on ketamine".

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The History of Ketamine



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Clinical use

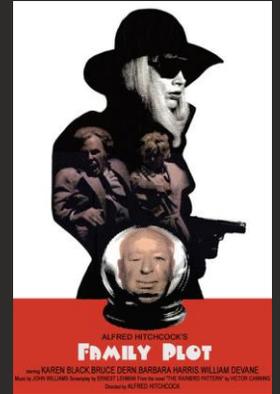
- Developed in the 1950s as an alternative pain-reliever to its chemical cousin, PCP
- Became available via prescription in the US in 1969 under the name Ketalar®
- Approved for human consumption by the FDA in 1970
- A good safety profile for its analgesic effects
- Used as a field anesthetic for soldiers during the Vietnam War
- Concerns over its hallucinogenic effects; was largely replaced by other hypnotics
- Still used outside the US in field conditions
- Used widely by EMS in the US
- Added to the World Health Organization's Essential Medicines List in 1985



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Early recreational use and 'abuse'

- Might have occurred as early as 1967
- Some reports suggest that available as pills and powder on the 'street' in the 1970s
- Introduced to pop culture in 1976
- Abuse first reported by the FDA in 1979
- By the mid-1980s, instances of addiction were reported



Siegel RK. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. *NIDA Res Monogr.* 1978(21):119-147.
 Jansen K. Ketamine: Dreams and Realities. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies; 2000.
 Ketamine abuse. *FDA Drug Bull.* 1979;9(4):24. Kamaya H, Krishna PR. Ketamine addiction. *Anesthesiology.* 1987;67(5):861-862.
 Jansen KL. Non-medical use of ketamine. *BMJ.* 1993;306(6878):601-602.

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Recreational use booms

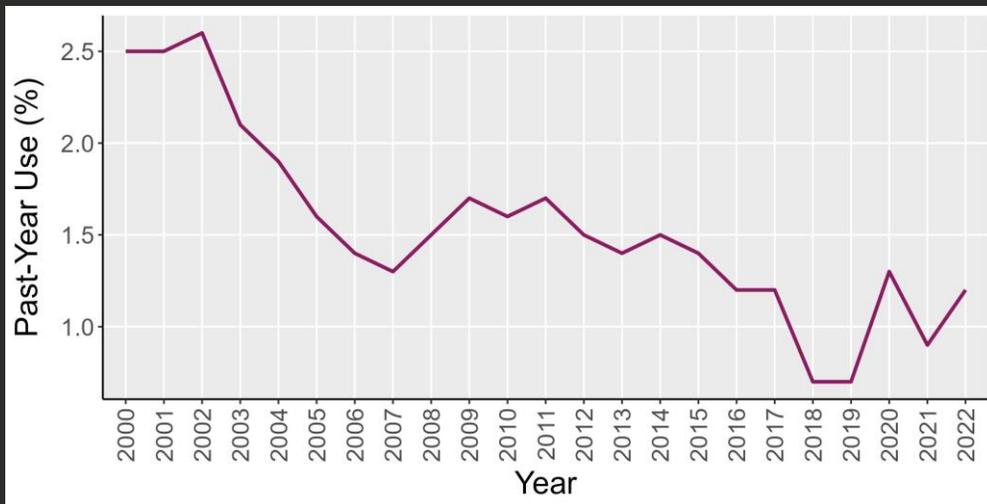
- Appeared in the nightclub scene in the early 1990s as an adulterant in ecstasy
- Soon after it became sold on its own
- Between 1992 and 1999, the DEA received ~800 reports of sales and possession
- Widespread diversion (veterinary clinics)
- Scheduled by the DEA (Schedule III) in 1999



Corben B. Limelight: The Rise and Fall of New York's Greatest Nightclub Empire 2011.
 Mion G. History of anaesthesia: The ketamine story - past, present and future. *Eur J Anaesthesiol.* 2017;34(9):571-575.

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Ketamine use among high school seniors in the US

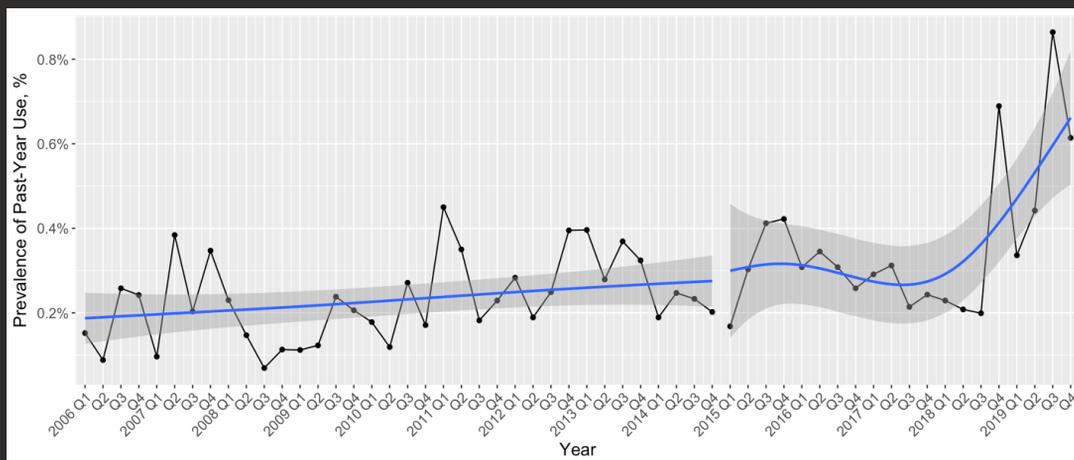


Miech RA, Johnston LD, Patrick ME, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975–2022: Secondary school students. Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan. 2023.



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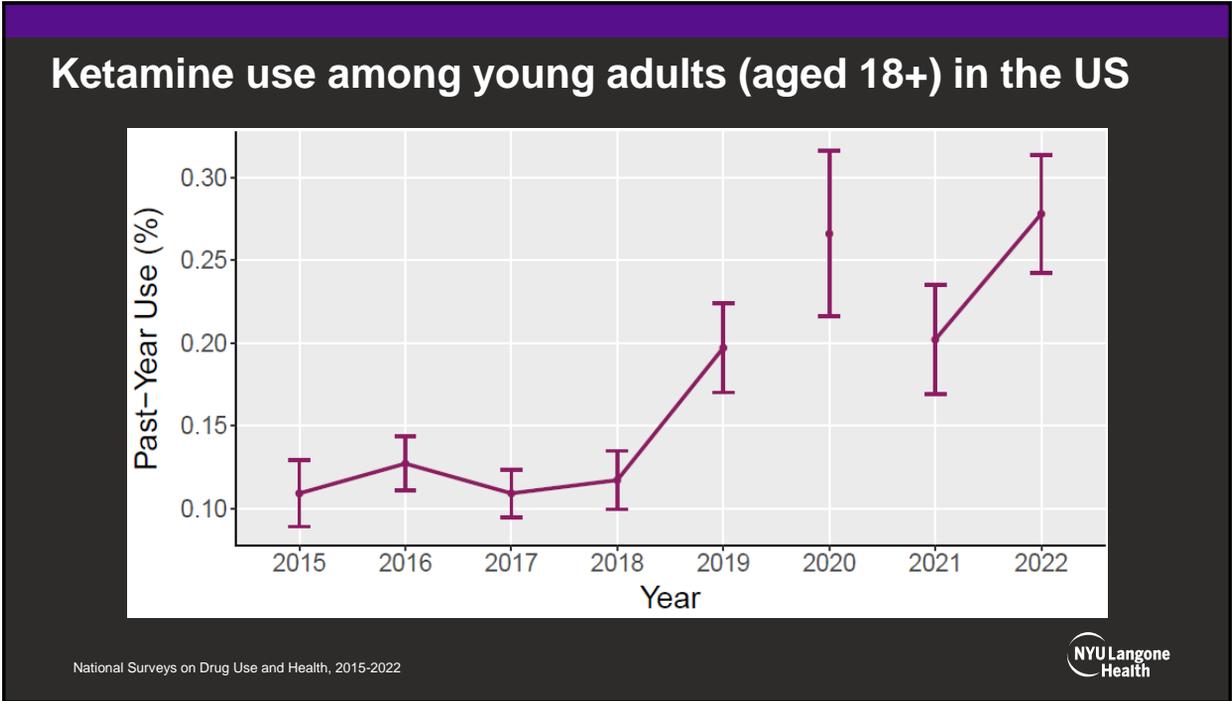
Ketamine use among young adults (aged 18-34) in the US



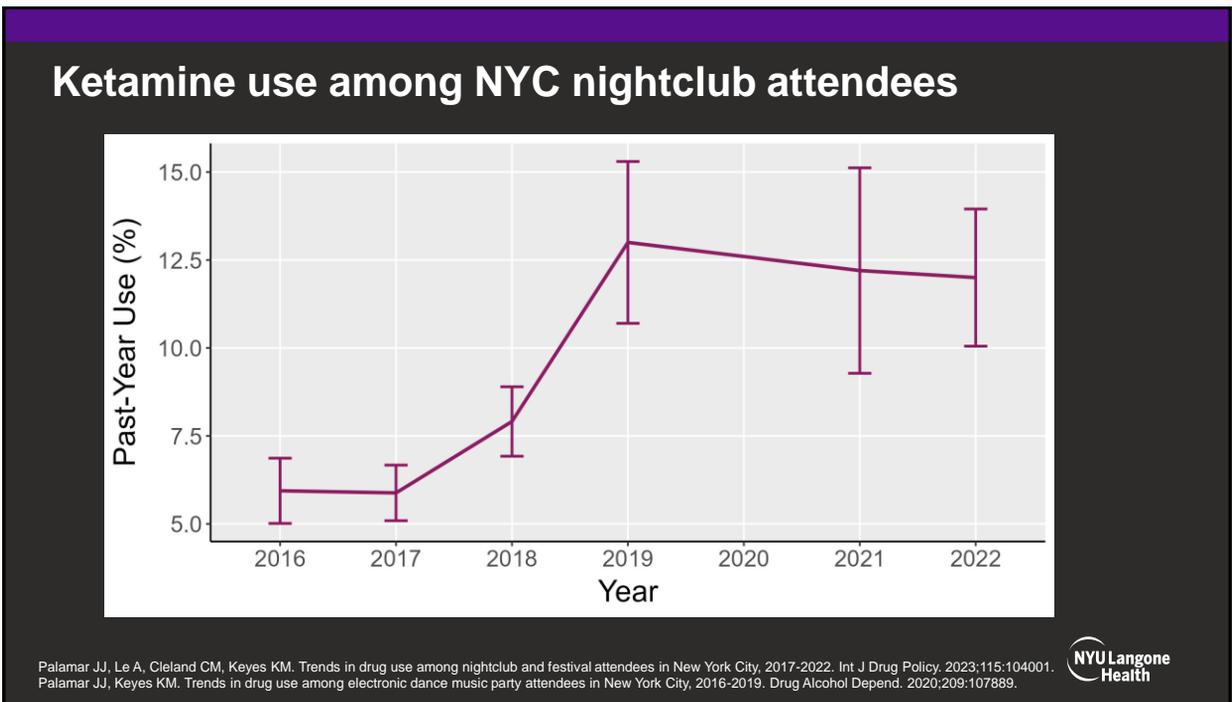
Palamar JJ, Rutherford C, Keyes KM. Trends in Ketamine Use, Exposures, and Seizures in the United States. Am J Public Health. 2021;111(11):2046-2049.



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Law enforcement seizures

- Decades ago, most ketamine was diverted from legitimate sources (e.g., veterinary clinics)
- Global production from clandestine laboratories in Southeast Asia (previously India)
- Most is now smuggled in through Mexico
- This version of ketamine is thus not pharmaceutical grade



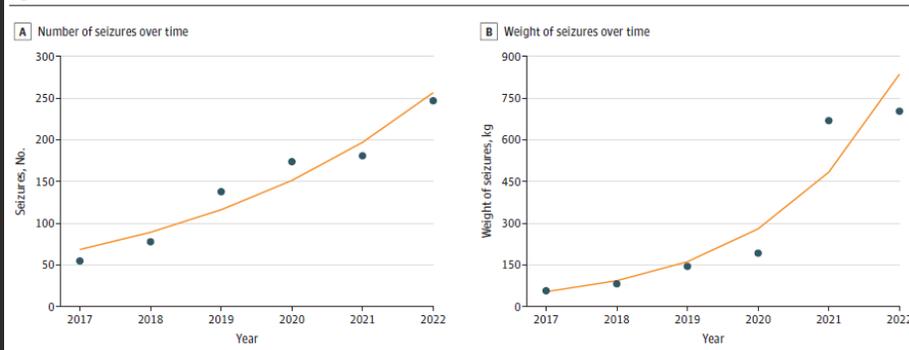
National Drug Intelligence Center. Intelligence Bulletin: Ketamine. July 2004. Cloud J. Recreational Pharmaceuticals. *TIME* 2001. Images: DEA. Ketamine. Erowid. Ttokkyo image. UNILAD. Hong Kong police seizure record 13-ton haul of ketamine.



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Ketamine law enforcement seizures in the US

Figure. Trends in Ketamine Seizures in the US From 2017 to 2022



- The number of seizures increased 349% from 55 in 2017 to 247 in 2022
- 824 seizures in total weighing 4,084 lbs. (with one seizure weighing 1,591 lbs.)
- 99% in powder form

Palamar JJ, Wilkinson ST, Carr TH, Rutherford C, Cottler LB. Trends in Illicit Ketamine Seizures in the US From 2017 to 2022. *JAMA Psychiatry*. 2023;80(7):750-751.



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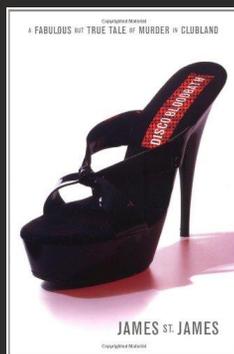
Effects



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“It pretzels your thoughts into Mobius strips.”
“You see everything inside and out and curling all around itself...
There’s a lot of unfolding.”

James St. James, *Party Monster*



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General effects

- Numbness, passiveness, and perception that the world is not real
- Changed perception of body consistency or distortion of body parts
- Sensations of weightlessness or floating
- Absence or distortion of a sense of time or place
- Even small doses can lead to dissociation and hallucination
- Larger doses can lead to intense detachment from reality and perceived out-of-body experiences (“K-hole”)
- Effects can be seen as pleasurable or *horrific*
- Effects can thus impair judgment and impede functioning



Hansen G, Jensen SB, Chandresh L, Hilden T. The psychotropic effect of ketamine. *J Psychoactive Drugs*. 1988;20(4):419-425.
 Jansen K. Ketamine: Dreams and Realities. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies; 2000.
 Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993-2006). *J Clin Psychopharmacol*. 2008;28(1):114-116.
 Image: flowvella.com. Ketamine.

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Adverse effects



- We found that a fifth (19%) of nightclub attendees who used ketamine in the past year reported a “harmful or very unpleasant” effect after use in which they were concerned about their immediate safety
- In our more recent study, 13% had experienced such an effect after use in the past month
- Of these, 59% asked someone for help and 7% visited an emergency department
- Confusion and nausea/vomiting were the most common symptoms
- The last year of Drug Abuse Warning Network data in 2011 estimated 1,550 ketamine-related ED visits in the US (with 71.5% of cases involving alcohol co-use)
- Preponderant in 278 overdose cases and 109 deaths reported in the literature

Palamar JJ, Acosta P, Le A, Cleland CM, Nelson LS. Adverse drug-related effects among electronic dance music party attendees. *Int J Drug Policy*. 2019;73:81-7.
 Palamar JJ, Le A. Prevalence of self-reported adverse effects associated with drug use among nightclub and festival attendees, 2019-2022. *Drug Alcohol Depend Rep*. 2023;7:100149. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. Rockville, MD: 2013. Chaves TV, Willfert B, Sanchez ZM. Overdoses and deaths related to the use of ketamine and its analogues: A systematic review. *Am J Drug Alcohol Abuse*. 2023; 49(2):141-150.

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Adverse effects

- In a study of ED presentations, the most common acute effects were impaired consciousness (45%), hypertension (40%), and tachycardia (39%)
- Acute risk of physical harm or death from accidents (e.g., drowning, car crashes)
- Vulnerable to physical and sexual assault
- Frequent ketamine use can lead to use disorder, driven by tolerance and craving
- Ulcerative cystitis, intense abdominal pain (“K-cramps”)
- Short- and long-term memory impairment
- Symptoms similar to symptoms of prodromal schizophrenia

Shbair MK, et al. Drugs involved in drug-facilitated crimes: Part I: alcohol, sedative-hypnotic drugs, gamma-hydroxybutyrate and ketamine. A review. *Ann Pharm Fr.* 2010;68(5):275-85. Fitzgerald ND, et al. Test-retest reliability and cross-cultural applicability of DSM-5 adopted diagnostic criteria for ketamine use disorders. *Drug Alcohol Depend.* 2021;228:109056. Morgan CJ, Curran HV. Ketamine use: a review. *Addiction.* 2012;107(1):27-38. Muetzelfeldt L, et al. Journey through the K-hole: Phenomenological aspects of ketamine use. *Drug Alcohol Depend.* 2008;95(3):219-29. Morgan CJ, et al. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. *Addiction.* 2010;105(1):121-33.



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‘Talented’ student, 18, died after taking ketamine on first day at university, inquest told



Megan Pollitt: Cardiff student died after ketamine and alcohol



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MATTHEW PERRY
DIED FROM 'ACUTE EFFECTS OF KETAMINE'

EXCLUSIVE 12/15/2023 1:25 PM PT

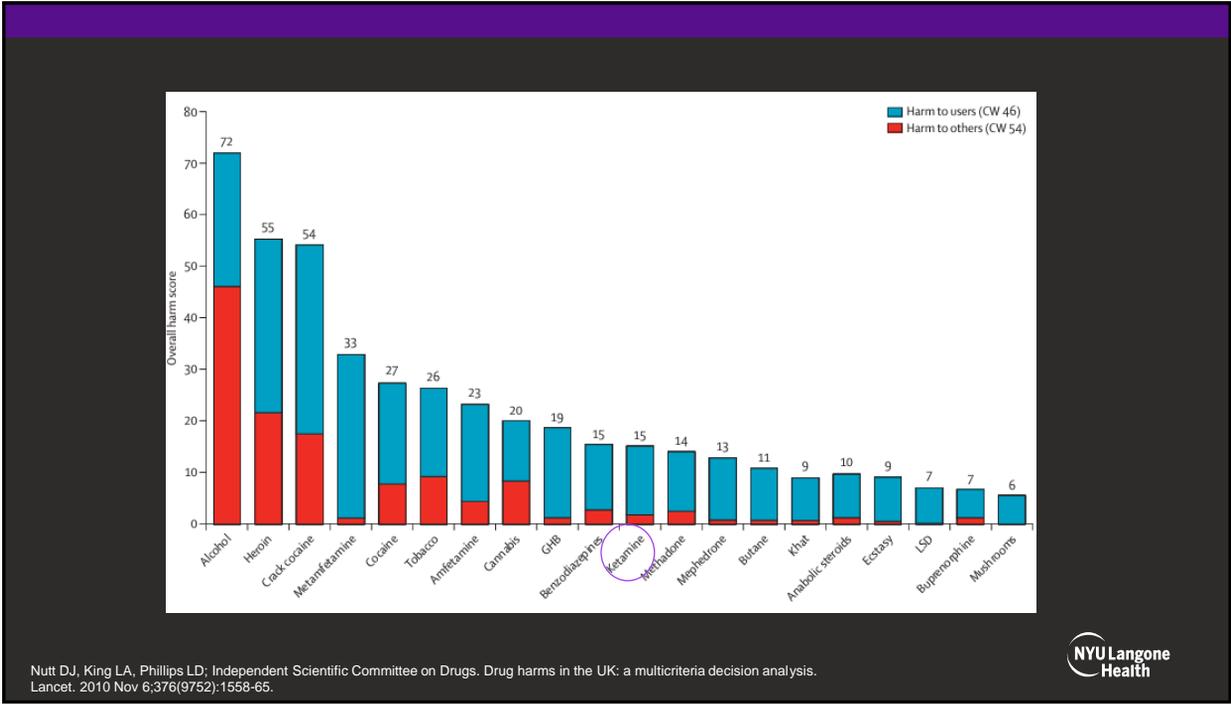
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Ketamine-related poisonings in the US

- 5% of cases reported to Poison Control in 2019-2021 were age ≤12 suggesting risk for childhood exposure

Palamar JJ, Rutherford C, Keyes KM. Trends in Ketamine Use, Exposures, and Seizures in the United States up to 2019. *Am J Public Health.* 2021;111(11):2046-2049.
 Palamar JJ, Fitzgerald ND, Grundy DJ, Black JC, Jewell JS, Cottler LB. Characteristics of poisonings involving ketamine in the United States, 2019-2021. *J Psychopharmacol.* 2023;37(8):802-808.

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Psychiatric Treatment

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Esketamine for psychiatric disorders

- In 2019, the FDA approved use of esketamine to treat treatment-resistant depression
- Esketamine (s-ketamine) is an enantiomer of racemic ketamine, sold as Spravato®
- Four times more potent than racemic ketamine, but good safety profile
- More expensive than most antidepressants, ~\$800 per treatment visit



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Esketamine adverse effects reported to the FDA

| Category | Number of Cases | % |
|--------------------------|-----------------|------|
| Dissociation | 1,011 | 16.3 |
| Suicidal Ideation | 640 | 10.3 |
| Sedation | 636 | 10.3 |
| Nausea | 431 | 7.0 |
| Depression | 419 | 6.8 |
| Vomiting | 360 | 5.8 |
| Anxiety | 346 | 5.6 |
| Dizziness | 296 | 4.8 |
| Hypertension | 262 | 4.2 |
| Blood Pressure Increased | 238 | 3.8 |
| Feeling Abnormal | 199 | 3.2 |
| Suicide Attempt | 196 | 3.2 |
| Hospitalization | 186 | 3.0 |
| Headache | 148 | 2.4 |
| Hallucination | 118 | 1.9 |
| Panic Attack | 115 | 1.9 |

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Off-label prescribing of (racemic) ketamine

- Ketamine (racemic) is *not* FDA-approved
- Off-label prescribing and over-prescribing by physicians *appears* to have increased
- Numerous clinics offer IV ketamine to treat depression and many other conditions:
 - Anxiety
 - PTSD
 - OCD
 - Neuropathic pain
 - Migraines
 - Rheumatoid arthritis
 - Lyme disease
 - Restless leg syndrome
 - Tinnitus
 - Cocaine use disorder



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Off-label prescribing of (racemic) ketamine

- Such treatment often has little to no evidence of efficacy
- Limited evidence on safety (immediate and long-term)
- No formal (post-marketing) surveillance of adverse events
- Not covered by insurance so treatment can be expensive
- Direct-to-consumer advertising
- Overemphasis of benefits
- High demand from patients
- A profit-driven environment without proper regulatory and legislative oversight

NEW YORK POST

Ketamine soars as pain, depression treatment — experts fear 'wild west' boom

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Is Ketamine Treatment Right For You?

OVERCOME OBSTACLES
KETAMINE THERAPY
for
ADDICTION

Hope & Relief
KETAMINE
INFUSION CENTER

A trip worth taking
Psychiatric Therapies.
Depression | Anxiety | PTSD
field trip health

Images: Ketamine SLC, Ketamine Therapy at Therapeutic Alternatives, Ketamine Infusion Center of LA, Seattle Times. As ketamine clinics emerge in Seattle to treat mental illness, so does debate about safety and regulations.

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JAMA Psychiatry | Special Communication

A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

- In 2017, several recommendations were made for ketamine prescribing, including:
- Provided by a clinician who can administer DEA Schedule III medications (in most states, this is a physician)
- Facilities should provide basic cardiac and respiratory monitoring and have a plan for providing stabilization and rapid transfer of patients with alterations in cardiac functioning
- Posttreatment assessments should confirm that the patient returns to a mental state that will allow for a safe return home

Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, Nemeroff CB; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry. 2017;74(4):399-405.

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Off-label prescribing of (racemic) ketamine

- In 2020/21, 98 clinicians surveyed throughout the US about off-label ketamine use
- 32% of teams did not have a physician on board
- 73% of teams did not have a psychiatrist on board
- 1-3% did not monitor vital signs
- 12-15% of those who monitored did not do so at least every 15 minutes

| Provider or Specialty Type | N | % |
|-----------------------------------------------|----|----|
| Administrating providers (N=98) | | |
| MD or DO only | 37 | 38 |
| Combination of providers with at least one MD | 29 | 30 |
| Certified registered nurse anesthetist | 25 | 26 |
| Registered nurse | 2 | 2 |
| Combination of providers without a MD | 5 | 5 |

O'Brien B, Wilkinson ST, Mathew SJ. An Update on Community Ketamine Practices. Am J Psychiatry. 2022;179(5):393-394.

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Free yourself from anxiety & depression with ketamine therapy.

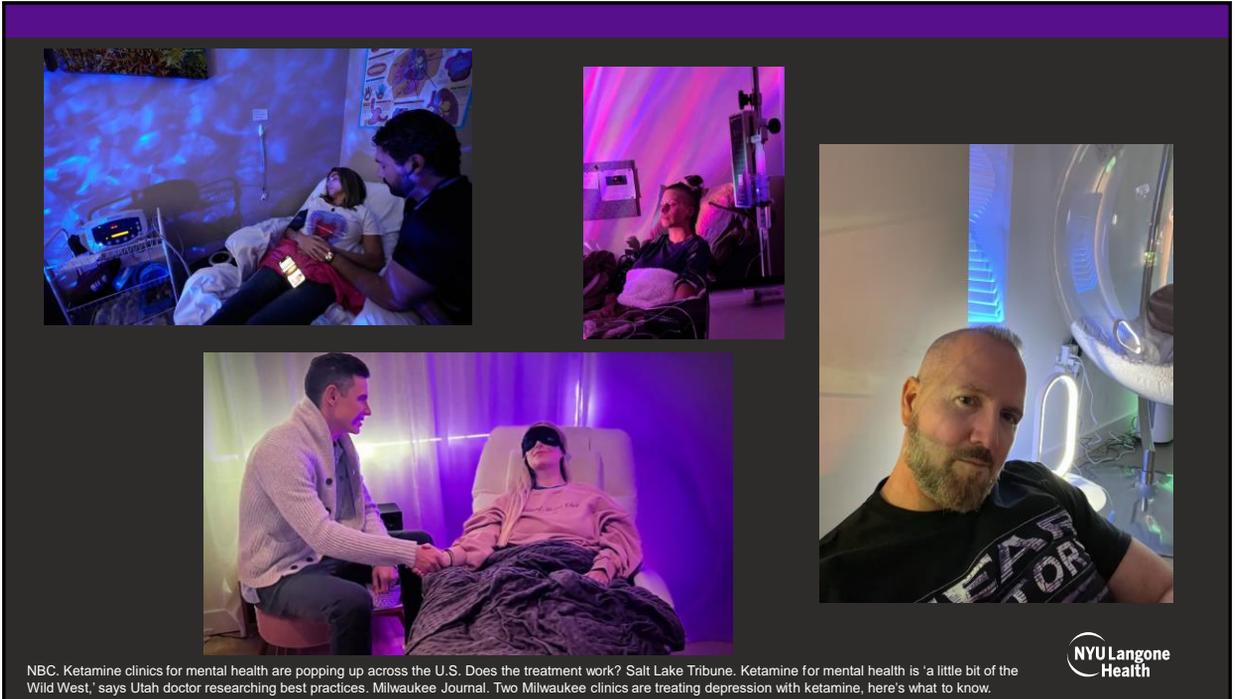
89% of patients in Mindbloom's largest-ever [therapy study](#) found relief from anxiety and depression symptoms.

"Mindbloom has changed my life. I've told anyone who will listen about ketamine therapy."
 ● Jennifer, Entrepreneur

Mindbloom.com



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Virtual prescribing

- Increased during the COVID pandemic
- Lozenges from compounding pharmacies
- In one study, very high dose (300-450 mg) rapid-dissolve tablets were mailed as a take-home treatment, with multiple tablets mailed to patients without recommended safety precautions
- One doctor had prescribed ketamine to over 3,000 patients in 44 states in just three years. The DEA shut down his clinic in 2023



Gilbert D. This doctor prescribed ketamine from his home. DEA shut it down. Washington Post. May 10, 2023.
Image: balancedmentalwellness.com. Psychotherapy with Ketamine Troches: Age Guidelines

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Risks associated with unsupervised use

- Dysphoric reactions at home without medical supervision
- Patients can harm themselves or others
- Iatrogenic use and unintended consequences of prescribing
 - Diversion
 - Stockpiling and taking large doses
 - Alternate routes of administration
 - Ketamine use disorder
 - Seeking illegal supply after introduced to the drug
 - Unlike other prescribed psychoactive drugs, ketamine 'street' price is much cheaper



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Media and Pop Culture



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'It saved my life': Relative of party drug 'Special K' could revolutionize depression treatment



Club drug spray ketamine can stop suicidal thoughts, study finds



Club drug Special K might be miracle cure for depression



The Club Drug Ketamine May Treat Depression- but the Risks Could Be Big



Could the Club Drug Ketamine Treat Depression?



'Club Drug' Ketamine Rescues Suicidal Patients: Study

A 'club drug' used as an anesthetic can help clear up the distraught thinking of people on the brink of suicide, researchers reported Tuesday.



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nature

'Party drug' turned antidepressant approaches approval

Club drug finds use as antidepressant

Psychedelic ketamine hits the blues surprisingly fast.



In dance clubs, the drug ketamine is popular for its mood-altering ability.

Party drug puzzles scientists

Ketamine can ease depression in hours, but researchers might have misjudged how it works.



Pills popped in a nightclub are potential therapeutics too.

How club drug ketamine fights depression

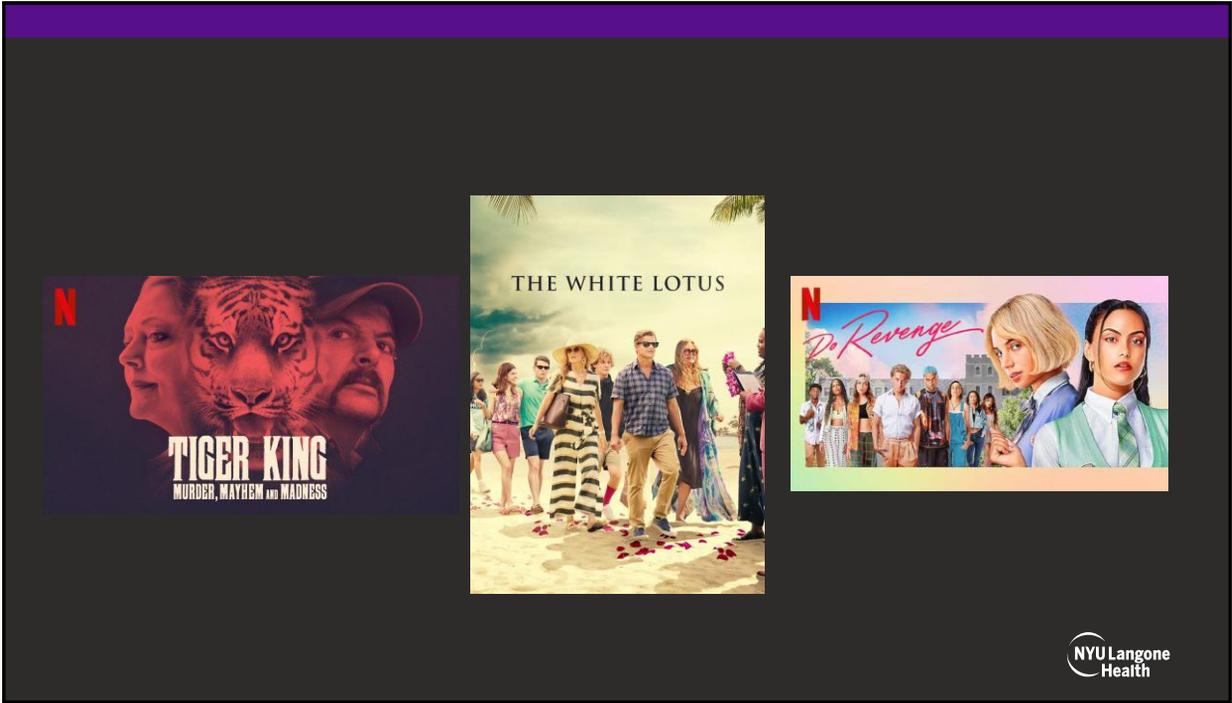
Breakdown product of drug reduces signs of depression in mice without side effects.

Heidi Ledford

04 May 2016



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Effects of media coverage?

- In our study of NYC nightclub attendees, 10% reported increased likelihood of using ketamine recreationally due to positive media coverage
- 6% of those reporting never having used would initiate use

Palamar JJ, Le A. Media coverage about medical benefits of MDMA and ketamine affects perceived likelihood of engaging in recreational use. *Addict Res Theory*. 2022;30(2):96-103.

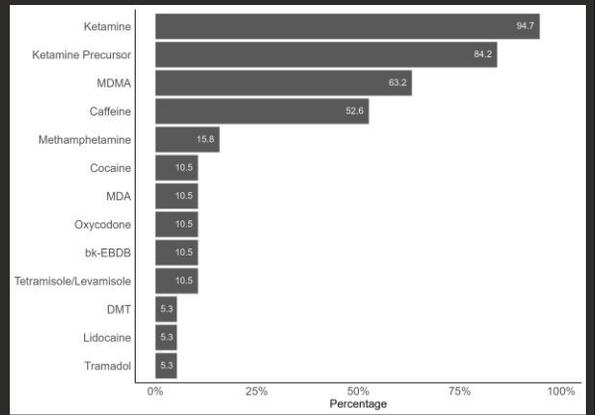
| Category | Percentage |
|---------------|------------|
| More Likely | ~10% |
| Less Likely | ~20% |
| Don't Know | ~25% |
| No Difference | ~45% |

| Category | Percentage |
|----------------|------------|
| Never Used | ~5% |
| Lifetime Use | ~25% |
| Past-Year Use | ~45% |
| Past-Month Use | ~55% |

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Tusi

- Tusi is a phonetic translation of the drug 2C (or 2C-B)
- Tusi, also sometimes referred to as “pink cocaine”, is a pink powder which almost always contains ketamine
- Most users likely have no idea what this mystery powder contains



Palamar JJ. Tusi: a new ketamine concoction complicating the drug landscape. *Am J Drug Alcohol Abuse*. 2023;49(5):546-550. Image: Mixmag, Mixmag Explores The Rise and Fall of “Tusi”.

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Continued Surveillance is Needed

- It is paramount to understand the drivers of ketamine use and acceptability and monitor legal and illegal ketamine use trends
- Research is needed to monitor the quickly changing legal and illegal ketamine landscape and to determine whether shifts in availability predict shifts in use, misuse, diversion, and adverse effects related to use
- Research is needed to determine how much off-label prescribed ketamine has reached the black market
- We need this information to inform:
 - Policy decisions (regarding regulation, control, and advertising)
 - Prevention (to educate people about risks associated with use)
 - Treatment (for those experiencing problematic use)
 - Harm reduction (informing ketamine use in a safer manner)

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Ketamine R01

Investigating the Ketamine Landscape



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Aim 1

Monitor ketamine prescribing practices and availability via legal channels and determine their effect on shifts in medical use and misuse, recreational use, associated adverse effects, and drug diversion

- Web-scaping to identify clinics
- Calling of veterinarians to monitor diversion
- Clinicians who prescribe ketamine (n=320)
- Patients who are prescribed ketamine (n=400)
- A particular focus on misuse, iatrogenic use (use leading to higher severity drug use including use of other drugs), adverse effects, and ketamine diversion



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Aim 2

Estimate trends, patterns, and correlates of ketamine use and severity of use by nightclub attendees and college students, and, among people who use ketamine in these samples, deduce exposure to adulterants such as fentanyl

- Nightclub attendees (N=3,200)
- College students (N=3,200)
- Time-space sampling
- Screener survey to estimate prevalence
- Full survey offered to people who use ketamine



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Aim 3

Estimate and compare trends in ketamine use and use severity, availability, and related morbidity and mortality in the tri-state area and determine whether trends of use and adverse events are predicted by increased prescribing of legal and availability of illegal ketamine

- Law enforcement seizures (indicating availability)
- Morbidity (poisonings)
- Mortality



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Acknowledgments

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Thank You

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