Conflicts

I declare no conflicts of interest

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National Institute on Drug Abuse:
- U01DA051126 (PI: Cottler)
- R01DA057289 (PI: Palamar)
The Rapidly Shifting Ketamine Landscape in the US

JAMA Psychiatry

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

The History of Ketamine

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
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

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

Ketamine use among high school seniors in the US


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

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

National Surveys on Drug Use and Health, 2015-2022

Ketamine use among NYC nightclub attendees

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

Ketamine law enforcement seizures in the US

- 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
Effects

“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
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

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
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

Ketamine-related poisonings in the US

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

Psychiatric Treatment
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Cases</th>
<th>%</th>
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<td>Dissociation</td>
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<tr>
<td>Suicidal Ideation</td>
<td>640</td>
<td>10.3</td>
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<tr>
<td>Sedation</td>
<td>636</td>
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<tr>
<td>Nausea</td>
<td>431</td>
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<td>Depression</td>
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<td>Vomiting</td>
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<td>Anxiety</td>
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<td>5.6</td>
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<tr>
<td>Feeling Abnormal</td>
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<tr>
<td>Suicide Attempt</td>
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<td>1.9</td>
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<tr>
<td>Panic Attack</td>
<td>115</td>
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Esketamine adverse effects reported to the FDA

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

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*
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
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


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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
NBC: Ketamine clinics for mental health are popping up across the U.S. Does the treatment work? Salt Lake Tribune. Ketamine for mental health is ‘a little bit of the Wild West,’ says Utah doctor researching best practices. Milwaukee Journal. Two Milwaukee clinics are treating depression with ketamine, here’s what to know.

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

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

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

NBC NEWS

Club drug spray ketamine can stop suicidal thoughts, study finds

NEW YORK POST

Club drug Special K might be miracle cure for depression

TIME

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

Men's Health

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 distressing thinking of people on the brink of suicide, researchers reported Tuesday.

nature

‘Party drug’ turned antidepressant approaches approval

Club drug finds use as antidepressant

Psychedelic ketamine hits the blues surprisingly fast.

How club drug ketamine fights depression

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

Heidi Ledford
04 May 2016
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.

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

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 need 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)
Ketamine R01
Investigating the Ketamine Landscape

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
**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

**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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Thank You

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