Podcast
Ketamine: A Re-emergence in Medicine and Misuse?

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What is Ketamine (Ketalar®, Spravato®)?

DEA Schedule III

Ketamine is used as an anesthetic, analgesic, antidepressant, and hallucinogen[1]

- Derivative of Phencyclidine (PCP)
- N-methyl-D-aspartate (NMDA) receptor antagonist and blocks HCN1 receptors[1,2]
  - **Analgesic** effects: At high doses it can bind to **Mu and Sigma opioid receptors**
  - Disrupts the neurotransmitter glutamate which is involved in learning, memory, emotion, and pain
- Ketamine hydrochloride injection available as prescription since the 1970s to induce **anesthesia**

Ketamine is NOT FDA approved for all psychiatric and mental health disorders

1. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (Spravato™) for use in treatment-resistant depression In conjunction with an oral antidepressant. *P T*. 2019;44(6):340-375.
2. Kobayashi NHC, et al. Ketamine plus alcohol: what we know and what we can expect about this. *Int J Mol Sci*. 2022 Jul;23(14):7800. doi:10.3390/ijms23147800

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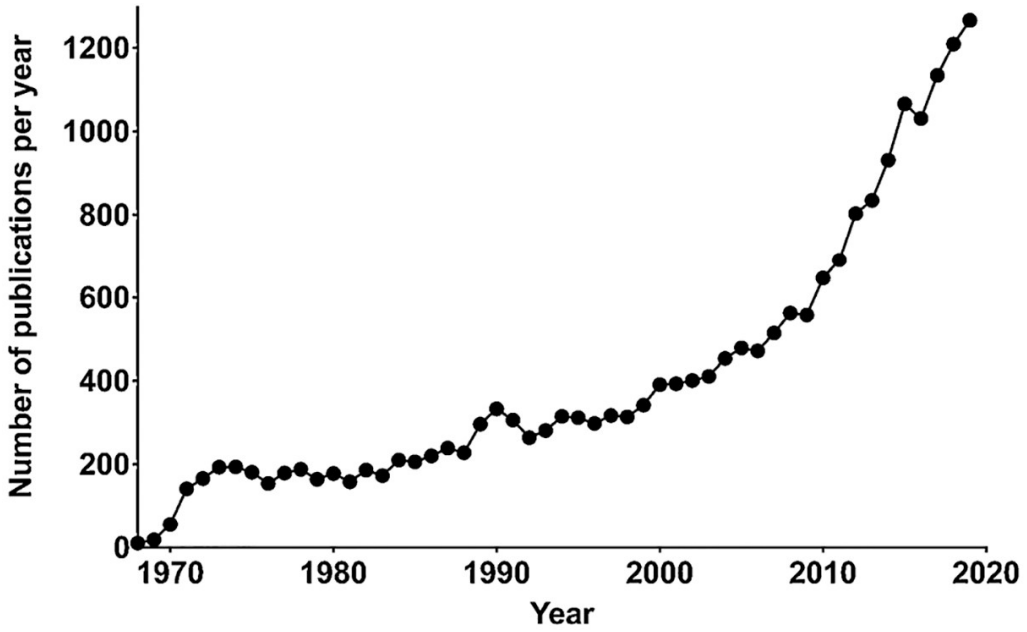
A re-emerging interest

DEA Schedule III

Not a novel substance but increasingly novel in human use!

- There has been a burst of research into ketamine to better understand the mechanisms that underlie its antidepressant effects[1]
- Number of publications on ketamine indexed in PubMed each year from 1965 to 2019, based on a simple keyword search.
- Note the upward incline beginning in the late 1990s, and then escalating in the past decade, illustrating the tremendous growth in research on the compound[1]

Trujillo and Iñiguez, p14



1. Trujillo KA, Iñiguez SD. Ketamine beyond anesthesia: Antidepressant effects and abuse potential. *Behav Brain Res*. 2020 Sep 15;394:112841. doi: 10.1016/j.bbr.2020.112841

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Major Depressive Disorder and treatment-resistant depression

FDA-approved intranasal antidepressant

- **Major depressive disorder (MDD)** affects more than **19 million adults** each year in the United States[1]
- World Health Organization (WHO): depression is the leading cause of disability worldwide[2]
- Many people treated on antidepressants have incomplete response or **Treatment-resistant depression (TRD)**
  - No positive therapeutic response after trying 2 or more antidepressant medications[3]
- Untreated depression is a major risk factor for **suicide**
  - Approximately 1 person every 40 seconds successfully completes suicide[4]
  - Incomplete response to traditional antidepressants led to research of novel substances to treat depression rapidly, particularly for those at risk of suicide

1. National Institute of Mental Health. *Major depression.* February 2019. Accessed December 10, 2021. https://www.nimh.nih.gov/health/statistics/major-depression.shtml.
2. WHO. Depression 2018. Mar 22, 2018. Accessed December 10, 202]. http://www.who.int/en/news-room/fact-sheets/detail/depression
3. Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychol Med.* 2010;40(1):41–50. doi:10.1017/S0033291709006011
4. WHO. National suicide prevention strategies:progress examples and indicators. January 19,2019. Accessed December 10, 2021. https://www.who.int/mental_health/suicide-prevention/national_strategies_2019/en/

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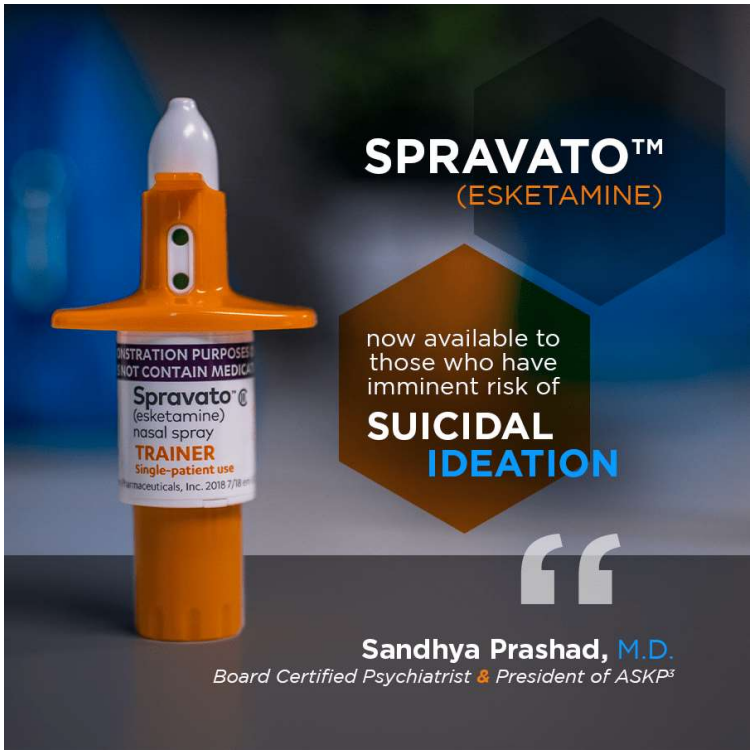
Intranasal Ketamine Isomer

Ketamine is NOT FDA approved for ALL psychiatric and mental health disorders

- **Randomized** double-blind controlled-placebo trials have recently determined that intranasal nonanesthetic doses of esketamine have an ultrarapid antidepressant effect
- **Esketamine (Spravato®)** nasal spray is the only version of ketamine that is FDA-approved (2019)
  - In conjunction with an oral antidepressant for
    - Treatment-resistant depression (TRD)
    - Depressive symptoms in adults with major depressive disorder (MDD) with suicidal thoughts or actions



Bahr R, Lopez A, Rey JA. Intranasal Esketamine (Spravato™) for Use in Treatment-Resistant Depression In Conjunction With an Oral Antidepressant. *P T*. 2019;44(6):340-375.

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Esketamine (Spravato®)

Intranasal antidepressant; FDA approved in conjunction with oral antidepressant for TRD and MDD

Ketamine reduces depression within 6 hours and effects lasting ≥ 6 weeks w/ other antidepressants.[1]

- Available with a **Risk Evaluation and Mitigation Strategy (REMS),** due to the potential for **sedation** and **dissociation**
- Self-administered under the **direct supervision** of a health care provider
- Patients must be **monitored** inside the healthcare setting after administration for a minimum of **2 hours** until patients are safe to leave
- S-ketamine or Esketamine has a higher affinity for the NMDA receptor and may produce fewer side effects such as drowsiness, lethargy, or cognitive impairment when compared to R-ketamine[2]
- **Intranasal**: Less invasive and less painful than injection and better bioavailability than oral ketamine[3-5]

1. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (SpravatoTM) for use in treatment-resistant depression In conjunction with an oral antidepressant. *P T.* 2019;44(6):340-375.
2. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry.* 2018;175(7):620–630. doi:10.1176/appi.ajp.2018.17060720
3. Covvey JR, Crawford AN, Lowe DK. Intravenous ketamine for treatment-resistant major depressive disorder [published online December 20, 2011] *Ann Pharmacother.* 2012;46(1):117–123. doi:10.1345/aph.1Q371
4. Malhi GS, Byrow Y, Cassidy F, et al. Ketamine: stimulating antidepressant treatment? *BJ Psych Open.* 2016;2(3):e5–e9. doi:10.1192/bjpo.bp.116.002923
5. Thomas R, Cetin M, Baker GB, Dursun SM. Comment on FDA's breakthrough therapy designation of intranasal esketamine for the treatment of major depressive disorder with imminent risk of suicide. *Klinik Psikofarmakol Bulteni.* 2016;26(4):329–331. doi:10.5455/bcp.20161027122045

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Ketamine Black Box Warning

FULL PRESCRIBING INFORMATION

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation

- **Patients are at risk for sedation after administration of SPRAVATO *[see Warnings and Precautions (5.1)]*.**

Dissociation

- **Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO *[see Warnings and Precautions (5.2)]*.**

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting *[see Warnings and Precautions (5.1, 5.2)]*.

Abuse and Misuse

- **SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse *[see Warnings and Precautions (5.3)]*.**

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS *[see Warnings and Precautions (5.4)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients *[see Warnings and Precautions (5.5)]*.

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Ketamine is not without risk

High-dose ketamine side effects

- Cardiovascular:
  - **Chest pain**
  - Increasing Heart Rate – **Tachycardia/Cardiac arrhythmia**
  - Increasing Blood Pressure - **Hypertension**
- CNS:
  - Amnesia
  - Coma
  - Delirium
  - Elevated Body Temperature
  - Fear
  - Panic
  - Seizures
  - Violent behavior
  - **Hallucinations or terrors (“k-hole”)**
- Respiratory:
  - **Respiratory depression** (with rapid high doses and if combined with other CNS depressants)
- Renal:
  - Kidney toxicity (with chronic abuse)
- Hepatic:
  - **Hepatotoxicity** in high dose IV admin in chronic pain patients
- GI:
  - Nausea
  - Vomiting

Not recommended in patients with cardiovascular issues or people at risk of psychosis

1. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (SpravatoTM) for use in treatment-resistant depression In conjunction with an oral antidepressant. *P T.* 2019;44(6):340-375.

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Ketamine is not without risk

- Should not be taken when patient is alone
  - Loss of motor coordination at moderate to high doses
  - If you were to fall and hurt yourself it would be difficult to call for help!
  - Imagine operating a vehicle—many states will consider it a DUI if driving under the influence of dissociative anesthetics such as PCP and ketamine
- Racemic ketamine, a combination of R and S ketamine, has been shown to cause **lesions in the brains** of rodents. The relevance of this finding to humans is still unknown[1]
- However, animal studies with S ketamine or esketamine (Spravato®) do not show this association.[1]

1. FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray. News release. US Food and Drug Administration. February 16, 2022. Accessed August 09, 2022. https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray

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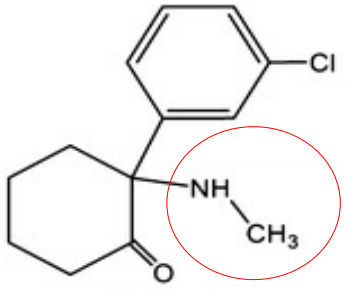
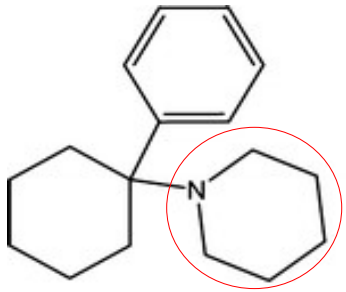
Why is ketamine **misused**?

Ketamine has dissociative hallucinogenic properties at high doses[1]

- Dissociative drugs may distort **sight, color, sound, and one's environment**
  - May produce "out of body experience"
- Related to phencyclidine (PCP)
- Injected, snorted, oral consumption
  - Often off-white powder; combined with cocaine: "Calvin Klein"
  - **50 mg–300 mg dose**
- Often used as a "club drug" at raves or festivals
- May be used as a "date-rape" drug to induce amnesia in unsuspecting victims



Ketamine



Phencyclidine

1. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (SpravatoTM) for use in treatment-resistant depression In conjunction with an oral antidepressant. *P T*. 2019;44(6):340-375.

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Trends in nonmedical use of ketamine: a “club drug”

Self-reported past year ketamine use increased 2006-2019 but remained relatively low ~1%[1]

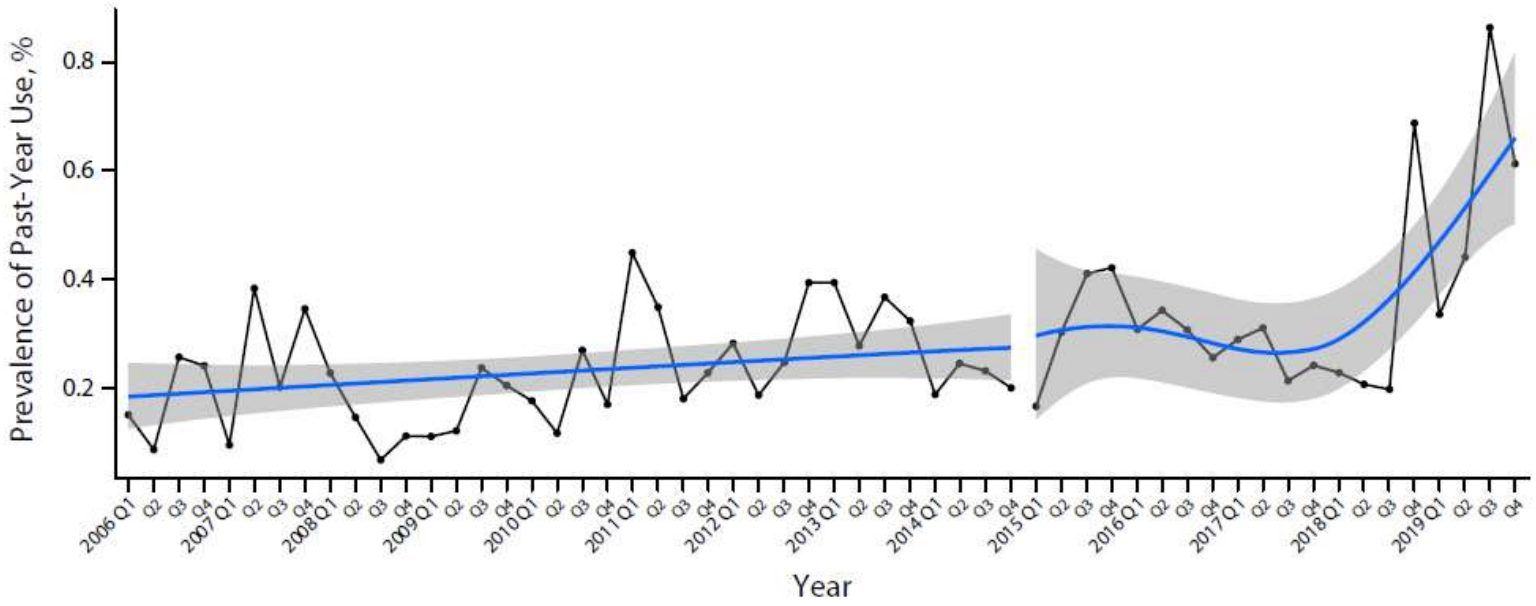

FIGURE 1— **Trends in Self-Reported Past-Year Ketamine Use, Aged 12–34 Years: United States, 2006–2019**

1. 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 Nov;111(11):2046-2049. doi:10.2105/AJPH.2021.306486

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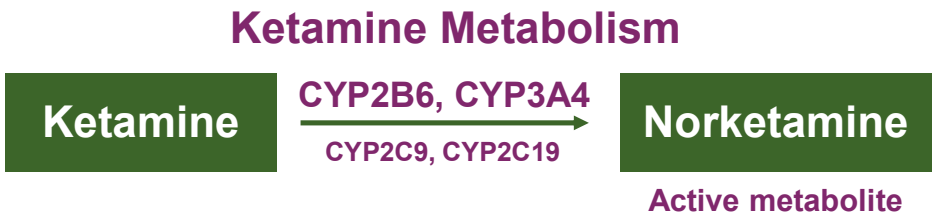
Do we test for ketamine?

Test Code 11831

Ketamine metabolism[1,2]

- Ketamine half-life (t1/2): ~45 minutes
- Eliminated from the body in 24 hours in most people
- Heavy users may excrete ketamine over longer periods of time.
- **Ketamine** and **norketamine** are detectable in urine drug monitoring



1. Bahr R, Lopez A, Rey JA. Intranasal Esketamine (SpravatoTM) for use in treatment-resistant depression In conjunction with an oral antidepressant. *P T*. 2019;44(6):340-375.
2. Adamowicz P, Kala M. Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: method and detection window considerations. *J Anal Toxicol*. 2005 Jul-Aug;29(5):376-82. doi: 10.1093/jat/29.5.376

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