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Psychiatry and Addictions Case Conference

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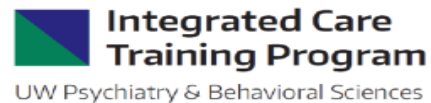
KETAMINE MISUSE

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WITH GUEST CONTENT EXPERT RYAN NYE, MD



SPEAKER DISCLOSURES

✓ Any conflicts of interest? None!

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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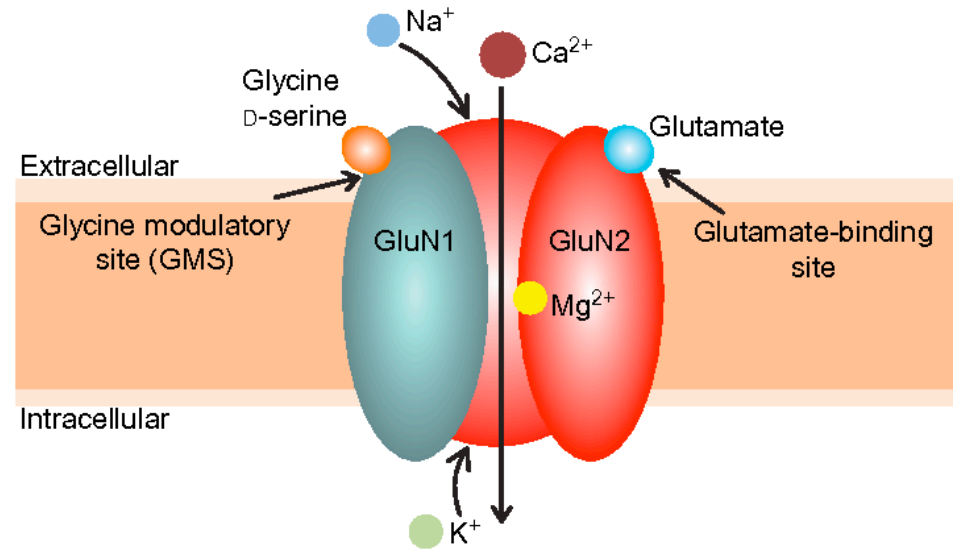
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OBJECTIVES

1. Learners will be able to apply knowledge of the general historical context of ketamine misuse to describe why ketamine misuse may be expected to increase in the U.S.
2. Learners will be able to identify sub-groups of patients/clients who are at higher risk for ketamine misuse and use this knowledge to provide those individuals additional screening, evaluation or treatment as appropriate
3. Learners will be able to educate their patients/clients about the most common physical and psychological co-morbidities resulting from ketamine misuse and screen for these in order to refer to appropriate additional specialty medical care as needed.

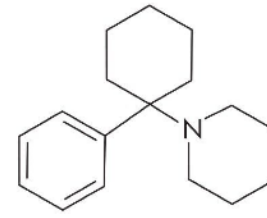
OVERVIEW

1. Brief History
2. Diagnostic Criteria
3. Risk Factors
4. Prevalence
5. Formulations and Dosing
6. Acute Effects
7. Chronic Effects
8. When to Consider
9. Treatment
10. Case Discussion
11. References

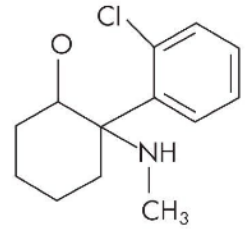


KETAMINE: A BRIEF HISTORY

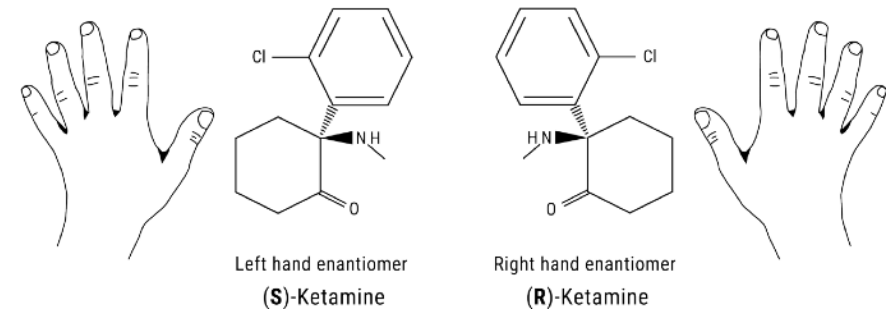
- 1962- Racemic ketamine synthesized from PCP while seeking safer anesthetic derivatives
- 1964- Tested in human volunteers
- 1966- Patented as anesthetic
- 1970- FDA approved racemic ketamine for anesthesia
- 1970s- Vietnam War battlefield anesthetic
- 1970- First cases of misuse/ addiction reported (started in 60's)
- 1980s- Misuse by medical personnel identified, then use as club drug
- 1990s- Global increase in recreational use
- 1999- DEA Schedule III Controlled Substance classification
- 2000- 2012- Misuse decreasing in the U.S.
- 2019- FDA approves intranasal esketamine as adjunct/ augmentation therapy for treatment resistant depression
- Current off-label therapeutic uses of ketamine
 - migraine, pain (refractory neuropathic, cancer, nociceptive), ECT, bipolar, schizophrenia, SUDs, asthma



1. Phencyclidine (PCP)



2. Ketamine (I.S.)



KETAMINE FORMULATIONS AND DOSING: THERAPEUTIC APPLICATIONS VS MISUSE OR DEPENDENCE

- Bioavailability: PO 17%, SL 29%, IN 50%, IM 90%, IV 100%
- Therapeutic Use:
 - Off-label: IV racemic ketamine 0.5mg/kg (about 45mg for a 200lb person per 40min infusion, 3x week x 6; Walsh et al 2022); oral racemic ketamine (delayed antidepressant effect); IV equivalent to IM for safety/effectiveness as depression treatment
 - FDA approved for TRD augmentation: IN esketamine (up to 84mg twice weekly)
- Recreational Use (racemic ketamine):
 - snorted in powder form (up to 95% of use) single doses 100mg-200mg (up to 500mg), from single dose sporadic use up to multiple grams (1-3 g) total daily, 3-5g daily use reported w/ withdrawal syndrome
 - Rare: liquid added to smoked materials or IM.
 - Healthcare providers may be more likely to use IV/IM
- 0.164grams vs 21 grams (128x)



REASONS FOR MISUSE

- Possible desired effects
 - Euphoria/rush
 - Sense of enhanced empathy/connection/group membership
 - Fit in with peers
 - Escape reality
 - Treat MH sx
 - Distortion of time (prolonged), space
 - Altered color perception
 - Enhancement of sexual experience
 - Reports of use in sexual assault
 - Detachment from body
 - ‘Out of body’ experience**
 - Change in sense of body ownership

What's a **“K-HOLE?”**

It's essentially a strong psychedelic episode that causes a complete sense of dissociation

Often caused by taking large doses of ketamine or by accumulation of smaller, frequent doses in a short period of time

PREVALENCE OF KETAMINE MISUSE

• United States

- Use by age/ education group
 - 12th graders 2000 - 12th grade 2.5%, 2012- 12th grade 1.5%
 - College students 2002 1.3%, 2005 1%, to 0.4% 2012
 - Young adults 2002 1.2% to 0.8% 2012
 - 2019 EDM parties in NYC 15% use (increased from 6% in 2016)

• Southeast Asia

- 2000- Entered Hong Kong at club drug to use with MDMA
- 2002- Solo club drug of choice in HK
- 2005- in Hong Kong the most common drug of abuse under age 21 (number of teens using ketamine doubled between 2005 and 2008 (Ng et al 2010). 2:1 M:F ratio. 3/4 used ketamine alone. Peak use in 2009, most popular substance from 2005-2014.

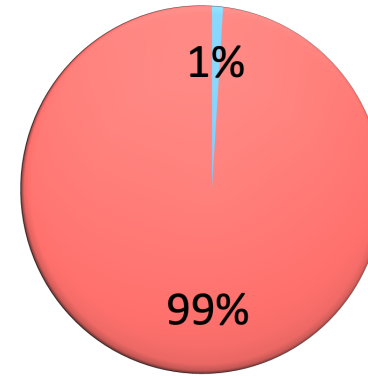
• UK

- England/Wales Peak levels of ketamine misuse from 2019-2020 GP 0.8%, 16-24 3.2%
- UK ketamine abuse 1.7% (lifetime use 4%)

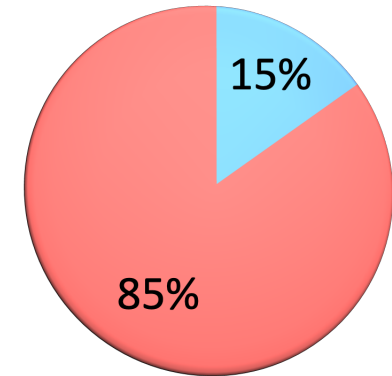
• Italy

- 1.1% students 15-19, 4% age 16-17, 5% age 18-25, 11% at raves/concerts
- 42% use ketamine alone
- Sedation more common in females (sex-specific hormonal effects)
- ED presentation: male, age 25, weekend ketamine use night/early AM

U.S. General



NYC EDM party scene



DIAGNOSING KETAMINE ADDICTION (DSM-5)

- **Phencyclidine Use Disorder**
 - “A pattern of phencyclidine (or a pharmacologically similar substance) use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
- Alternative: **Other Hallucinogen Use Disorder**
 - “A problematic pattern of hallucinogen (other than phencyclidine) use...”
- Standard SUD criteria with exception of absence of withdrawal signs/symptoms
 - Withdrawal syndrome not well established for PCP/ketamine/hallucinogens generally
- Specifiers: Specific hallucinogen, severity, remission status
- Other related conditions: Substance-Induced Mood Disorder (more common), Substance-Induced Psychotic Disorder (less common)

RISK FACTORS FOR KETAMINE MISUSE

- Access/ Availability
 - Medical providers: veterinary medicine, anesthesia specialists
 - East and Southeast Asia (Low cost racemic ketamine)
- Subculture
 - Raves, dance parties, nightclubs
- Youth
- Perceived Safety
- Male sex
- Other substance use (Heavy methamphetamine use, LSD use)

ACUTE EFFECTS OF KETAMINE: THERAPEUTIC DOSES (TIME TO RESOLVE)

- **Psychiatric/ Neurologic Symptoms**

- Increase in anxiety (2hrs)
- Dose dependent dissociative effects (2hrs)
- Dose dependent psychotomimetic effects (2hrs)
 - Unusual thought content, VH, AH, disorganized thinking (2hrs)
- Sedation, agitation, dizziness, blurry vision, delirium, irritability, sensory changes, vertigo (1-2hrs)
- With bipolar disorder: transient manic or hypomanic sx (80min)

- **Physical Symptoms**

- Mild, transient increase in blood pressure (30-120min)
- Heart rate changes (higher doses)
- N/V, HA, dry/numb mouth (1-2hrs)
- With pre-existing cardiac condition: Afib, ventricular extrasystoles



ACUTE EFFECTS OF KETAMINE: RECREATIONAL / DEPENDENCE DOSES

- **Neurologic symptoms:** Impaired consciousness (AMS with confusion, sedation, agitation), ataxic gait, slurred speech, mydriasis, tremors, blurred vision
- **Psychological symptoms:** panic attacks, delusions, hallucinations
- **Physical Signs/ Symptoms:** Acute liver injury/ elevated transaminases, nausea/vomiting (esp first time), hypertension, tachycardia, chest discomfort, palpitations, increased muscle tone, rhabdomyolysis, dry mouth
- **Laboratory Abnormalities:** Leukocytosis (1/3), elevated CK (1/3), transaminitis (1/6, HK ED n=233)
- **Accidental Injury**
 - **Greatest risk of death due to reduction of environmental awareness, inability to protect self**
 - most common trauma complication in ketamine related ED visits in Northern Italy were injury 2/2 falls and cuts 7%
- **Intentional Self-Injury**
 - 10% of ketamine-related visits in N Italy for suicide attempts, higher risk with comorbid opioid or stimulant use, N Italy ED n=74

- Rivas-Grajales et al 2021, Pavarin et al 2019, Ng et al 2010

KETAMINE OVERDOSE RELATED DEATHS IN THE MEDIA



1996



2019

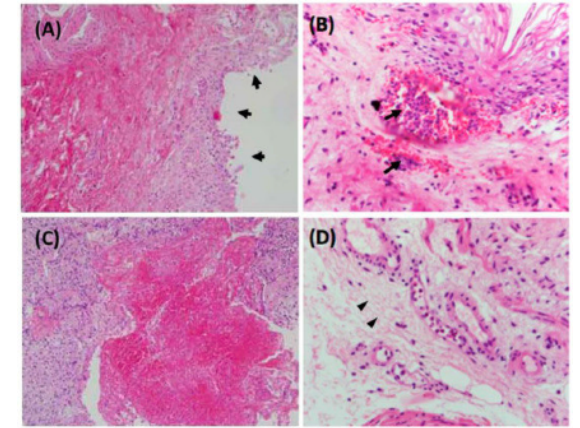


2023

CHRONIC EFFECTS OF KETAMINE MISUSE

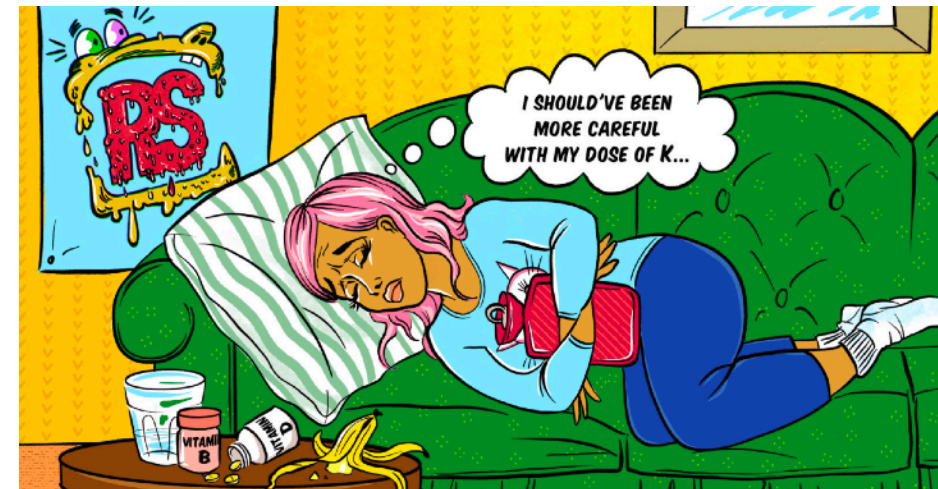
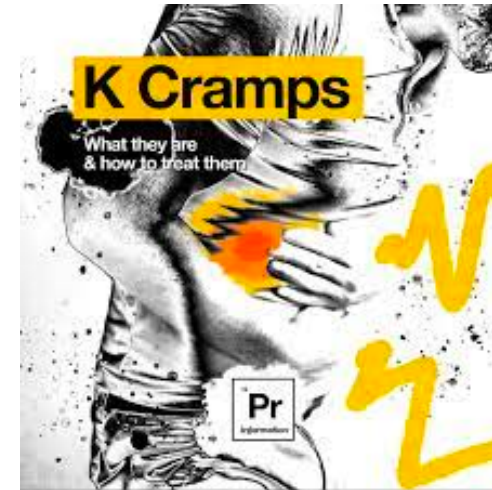
DOSE-DURATION RELATIONSHIP

- **Cognitive Impairment**
 - Speed of comprehension, verbal fluency
 - **Executive fxn:** Perseveration errors, word recall
 - **Memory:** working, short, and long term
 - Anatomic brain changes- lower gray matter volume, less white matter integrity, lower functional thalamocortical and corticocortical connectivity (2-10yes, 2.4g/day, Strouss et al 2022)
- **Persistent Psychiatric Symptoms**
 - **Depression** (most common)
 - Rarer: persistent dissociation/ delusional thinking
- **Abdominal pain**
 - 'K-cramps' Vague to intense, colicky
 - Gastritis
- **Hepatobiliary Injury**
 - Dilated common bile ducts
 - Liver injury
- **Bladder (LUTS) and Kidney Injury**
 - Ulcerative cystitis first reported 2007
 - Urinary pain and discomfort, frequency, hematuria
 - UA: Sterile, WBC, RBC. BMP: elevated CK
 - Lower voided volumes
 - Submucosal fibrosis, Collagen accumulation, contracted/thickened bladder walls**
 - Inflammation may extend to adhesion to the peritoneum
 - Hydronephrosis



PROGRESSION FROM KETAMINE MISUSE TO DEPENDENCE

- **Rapid development of tolerance to anaesthetic/pain effects**
 - Painful medical conditions ‘k-cramps’, gastritis, cystitis, biliary pain
 - Increasingly brief relief with increasing doses of ketamine
- **Significant depressive symptom**
 - Worsening within 1-2 days last dose
- **Psychological addiction**
 - Attentional bias to ketamine cues
- **Physical withdrawal syndrome**
 - autonomic arousal, ~ 4g/day per year
 - Shaking, sweating, palpitations
 - Restlessness, nightmares, hallucinations
 - Chills, lacrimation



WHEN TO CONSIDER KETAMINE MISUSE

- **Patient discloses- Ask!**
- **Risk factors for ketamine misuse**
 - Healthcare professional, young adult involved in related subculture, other substance use disorders
- **Physical signs/sx** associated with ketamine misuse without other explanation
 - HTN, tachycardia, upper or lower abdominal pain, gastritis, cystitis (resistant to antibiotics/ other tx), biliary tract dilation, evidence of snorting of powder (check nasal cavity)
- **Unexplained lab abnormalities** that decreases with time in controlled environment
 - UA revealing sterile pyuric or hemorrhagic cystitis,
- **Young person with depression, memory loss, frequent urinary complaints**
- **With existing ketamine prescription:**
 - PDMP w/ ketamine Rx from multiple providers, reporting lost medication, early refill requests, dose escalation/ frequency increase requests without clinical indication (Swainson et al 2022)

TREATMENT FOR KETAMINE MISUSE

- **Cessation of Ketamine Use**
 - SUD Treatment
 - Limited ketamine specific services (psychotherapy for youth developed in HK)
- **Treatment for depression**
- **Aggressive Pain Management**
 - For related medical conditions if pain driving frequency of use
- **Management of ketamine-induced cystitis**
 - First line: NSAID, COX-II inhibitors, paracetamol, phenazopyridine (70% respond)
 - Second line: Opioids, pregabalin (68% respond)
 - Third line: Intravesicular injections of urothelium protective agents
 - Sodium hyaluronate (5/8 completing reduced need for PO meds)
 - Fourth line: Surgery (outcomes poor)

CASE DISCUSSION

- Reminder to **stop recording** for an open discussion of a sensitive topic

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