Ketamine and Opioid Use Disorders

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Ketamine

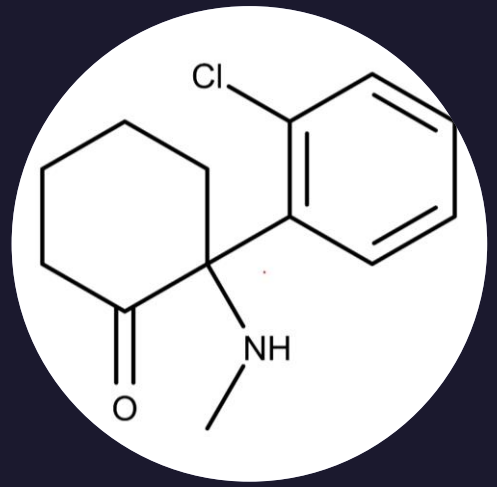
Background

Risks of Ketamine Use

Treatment of Ketamine Use Disorder

Relation to Opioid Use Disorder

Case Presentation



Background

How Ketamine Use Disorder Began

Background

ORIGINS

- Synthesized in 1962 as a replacement for phencyclidine (PCP) as an anesthetic
- Good safety data and is an anesthetic without respiratory suppression
- WHO has labeled it an essential medicine since it can be used without electricity and supplemental oxygen

IN SOCIETY

- The first reports of non-medical ketamine use were in the 1960s
- Expended use in the 1990s in Europe at “raves” as an adulterant to ecstasy
- Commonly use in South-East Asia
  - The single most abused drug in Hong Kong
- Becoming more popular

Background

ORIGINS IN MENTAL HEALTH

- First use as treatment of mental health in 1970s
- Formal investigation for off-label mental health treatment in 1990s

RECENT

- Research for a broad range of applications has exploded over the past 20 years
- FDA approved intranasal esketamine in 2019 for treatment-resistant depression
  - S-enantiomer
  - Spravato
- R-enantiomer now getting some attention

Background - Psychotherapy

- Synergistic with psychological therapies
  - Ketamine-assisted psychotherapy (KAP)
  - Both individual and group psychotherapy
  - CBT prolongs antidepressant effects of ketamine
- Psychedelic dosing makes therapy more effective (“Mystical Experience”)

Mechanisms of Action

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST

- Also:
  - Blocks nicotinic acetylcholine ion channels
  - Increased dopaminergic and noradrenergic neuromodulation
  - Weak agonist of delta and mu opioid receptor

NET EFFECTS

- Increases neural plasticity
- Disruption of functional networks
- Rapid antidepressant effects
- Reconsolidation
- Psychedelic effects

Routes of Use

MEDICAL

- Primarily intravenous
- Intranasal
- Intramuscular
- Oral

NON-MEDICAL

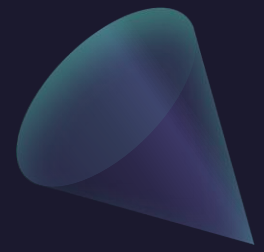
- Primarily in powder form
- Snorting/inhaling
- Less commonly intramuscular/intravenous
- Rarely orally
    - More sedative and less psychedelic

Intoxication

SUB-ANESTHETIC DOSES

- Low sub-psychedelic dose: empathogenic experience “K-Land”
- Medium psychedelic dose: out-of-body experience “K-Hole”
- High doses: dissolution of boundaries between reality and self (“near death experience”) “K-Hole”

REPORTED EFFECTS



- Melting into the surroundings
- Visual hallucinations
- Giggliness
- Dissociation to the point perceptions are completely detached from reality

Intoxication

OTHER EFFECTS

- Antidepressant
- Reduction in suicidal ideation
- Delirium
- Delusions
- Confusion

PSYCHOSIS LIKE

- Ketamine has been used as a pharmacological model of schizophrenia
  - Neuroimaging in healthy humans and rats
  - Pharmacological research

Withdrawal

PSYCHOLOGICAL

- Cravings
- Ongoing debate if other signs present
  - Depression
  - Anxiety

PHYSICAL

- Ongoing debate if any signs present
  - Shaking
  - Sweating
  - Palpitations

Risks of Ketamine Use

How Ketamine Addiction Affects the Body and Mind

Acute Use

OVERDOSE

- Incredibly difficult to accomplish
- 25x usual recreational dose
  - Recreational dose of 175 mg
  - 4.2 grams for 70 kg human
- No respiratory suppression
- Coughing and swallowing reflex maintained

CARDIAC RISK

- High blood pressure
- Tachycardia
- Compounded by coingestion of stimulants

Acute Use

COGNITIVE IMPAIRMENT

- Working memory
  - Allows the brain to hold onto information for a brief period of time while doing something else
- Episodic memory
  - Recollection of personal experiences or events
- Verbal learning
  - Learning from a lecture
- Spatial memory
  - Remembering where things are

Acute Use

ACCIDENTAL DEATH

- Highest source of mortality
- Anesthetic

HARM REDUCTION

- People intoxicated with ketamine should not be left alone
- People intoxicated with ketamine should be accompanied by someone who is sober

Chronic Use

ULCERATIVE CYSTITIS

- Urinary frequency
- Dysuria
- Painful hematuria

KIDNEY

- Hydronephrosis
- Papillary necrosis
- Renal failure has been documented

Chronic Use

K-CRAMPS

- Abdominal pain
- Further use of ketamine can alleviate the pain
- Lore is this is the result of swallowing postnasal drip
- CT demonstrated cystic dilation of common bile duct
- Liver damage/fibrosis

PSYCHOLOGICAL

- Increased depression found in daily users
- Prodromal schizophrenia syndrome in daily users
- Delusions
- Dissociation

Chronic Use

NEUROLOGIC

- Changes in temporal lobe
- Upregulation of dopamine receptors

COGNITIVE IMPAIRMENT

- Short-term memory
- Long-term memory
- Reversible

Chronic Use

ADDICTION

- Increased release and inhibited uptake of dopamine in nucleus accumbens
- Interacts with opioid receptors promoting rewarding properties
- Short half-life (1-2 hours)
- Compulsive use
- Tachyphylaxis

- Lower education
- Unemployment
- Increased health care utilization
  - Ulcerative cystitis

Ketamine Use Disorder Treatment

Managing complications and the underlying cause

Treatment

USE DISORDER

- No specific treatment
  - Modulation of glutamatergic system
  - Lamotrigine helped in one case study
- Behavioral and cognitive interventions
  - Cravings and compulsive use

COMPLICATIONS

- NSAIDs
- Anti-inflammatory medications
- Steroids
- Anticholinergic medications
- Urinary diversion and nephrectomy
- Abstinence

Ketamine and Opioid Use Disorder

What we know about treatment

Comorbid Ketamine and Opioid Use Disorders

LARGELY AN UNKNOWN

- The epidemiology appears to be unknown
- Polysubstance use with Ketamine use disorder is the rule rather than the exception
- Research has focused on treatment of opioid use disorder

Theoretical Prevention of Opioid Use Disorder

PAIN MANAGEMENT

- Reduces perioperative reduces cumulative opioid consumption
- Intravenous ketamine infusions for chronic pain management

OUTPATIENT PRESCRIPTIONS

- Reduces respiratory suppression
- Prevents hyperalgesia
- Lowers needed dosage

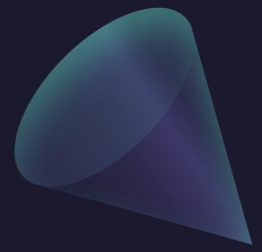
Opioid Withdrawal

CASE REPORTS

- Treatment of buprenorphine precipitated opioid withdrawal
- Wean from high dose outpatient prescription
- Anecdotal reports

STUDIES

- Reduced withdrawal scores



Treatment of Opioid Use Disorder

POTENTIAL MECHANISMS

- Glutamate dysfunction is implicated in addiction
- Promotion of neuroplasticity
- Restoration of glutamate imbalance and forming new synapses promotes learning new behaviors

- Decreased cravings
- Improves opioid withdrawal symptoms
- Antidepressant
- Enhanced motivation for changing problematic behaviors

Treatment of Opioid Use Disorder

KETAMINE PSYCHOTHERAPY

- Krupitsky and Grineko studied existentially oriented psychotherapy in 2002
- Psychedelic dose vs sub-psychedelic dose of ketamine

SPECIFIC TREATMENT PROCEDURE

- 10 hours of psychotherapy before to prepare patients
- 1.5-2 hours ketamine session
  - Emotional support
  - Individual and personality problems focused
- 5 hours of psychotherapy after to interpret and integrate their experiences into everyday life

Treatment of Opioid Use Disorder

KETAMINE PSYCHOTHERAPY

- Psychedelic dose vs sub-psychedelic dose of ketamine worked as anticipated
- Higher rate of abstinence at 24 months for psychedelic dose

- Decreased cravings
- Decreased anhedonia
- Decreased anxiety
- Decreased depression
- Increased internal locus of control
- Increased meaning and purpose of one's own life
- Increased spirituality
- Improved attitude towards abstinence

Treatment of Opioid Use Disorder

KETAMINE PSYCHOTHERAPY

- Krupitsky and Grineko then studied single vs multiple sessions in 2007

SPECIFIC TREATMENT PROCEDURE

- All given psychedelic doses
- Single session vs three sessions in monthly intervals
- 5 hours of psychotherapy before and 5 hours after for the first session
- The multiple session group had one hour of addiction counseling before and after the second and third sessions

Treatment of Opioid Use Disorder

KETAMINE PSYCHOTHERAPY

- There is a dose-response relationship
- The same improvements were seen
- Three sessions had an abstinence rate of 50% at one year as compared to 22.2% for the single session

Alcohol Use Disorder

KETAMINE PSYCHOTHERAPY

- Combined with aversive therapy, 70% abstinent at 12 months vs 24% aversive therapy alone
- KAP 66% abstinent at 12 months vs 24% conventional psychotherapy
- Combined with MI, 75% abstinent at 6 months vs 27% midazolam + MI

WITHDRAWAL

- Appears to be safe and effective as adjunctive treatment for alcohol withdrawal
  - Effective for benzodiazepine-refractory alcohol withdrawal
  - Decreased rates of intubation
  - Decreased days in ICU
- Theoretically beneficial for combined opioid and alcohol withdrawal

Cocaine Use Disorder

KETAMINE PSYCHOTHERAPY

- Combined with mindfulness-based behavioral modification, 48% abstinent at 14 days vs 11% with midazolam
  - 44% abstinent at 6 months vs 0% with midazolam

JUST INFUSIONS

- A single infusion reduced cocaine self-administration by 67% compared to baseline in non-treatment seeking individuals
- Three infusions:
  - Increased motivation to quit
  - Reduced cue craving and use at 4 weeks
- One study reported the mystical, but not dissociative, effects mediated efficacy

Future Treatment of Opioid Use Disorder

ONGOING RESEARCH

- Ketamine-assisted psychotherapy for opioid use disorder
- Ketamine for OUD and comorbid depression
- Ketamine for the treatment of opioid use disorder and depression

Case Presentation

One example of severe ketamine use disorder

Case Report

MR. A

- Presents for inability to discontinue ketamine use for >1 year
- 25-year-old salesman
- Had been using for 3 years
  - Initially via smoking and now snorting
  - Using 6-10 times daily
- Has uncreative cystitis and K-cramps
- Marked functional impairment and physical consequences

Case Report

PRIOR TREATMENT

- Two prior inpatient treatments
  - Had reported withdrawal of dysphoria, severe anxiety, and cravings
  - Achieved abstinence in a controlled environment
- Relapsed soon after discharge

LAMOTRIGINE

- Titrated during his third hospital stay
- Blocked the positive feelings associated with ketamine
  - Instead, experienced dizziness, fatigue, nausea, and headaches
- Decreased use to 2-3 times daily and using 1/5th total daily dose
- Occupational functioning stabilized

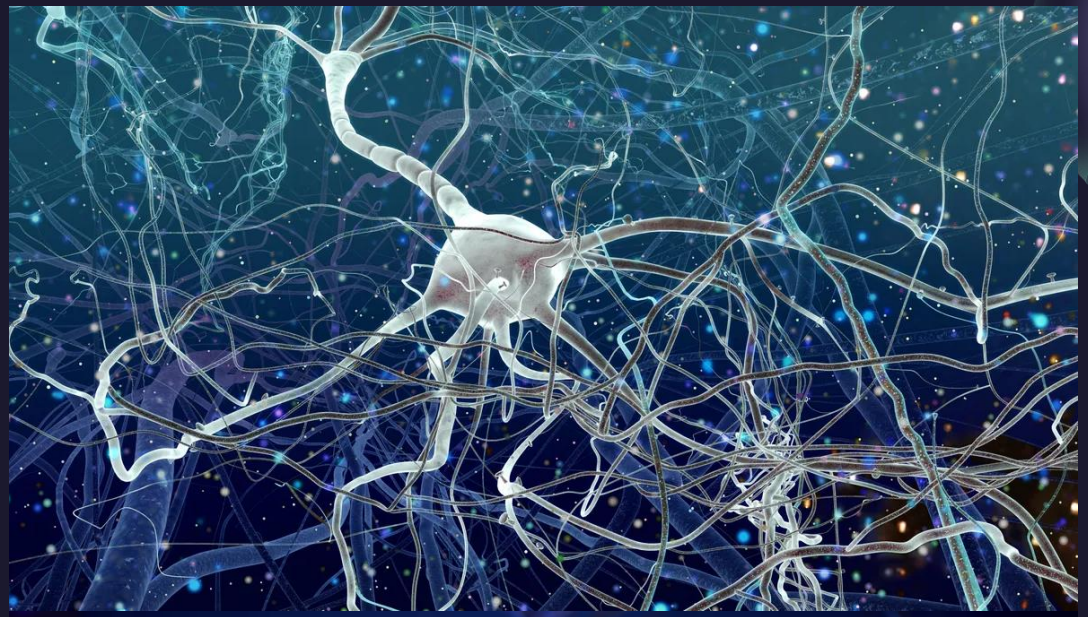
Case Report

END RESULT

- Took lamotrigine for 3 months
- Ultimately stopped lamotrigine to again experience the positive effects of ketamine
- Did not receive outpatient therapy

Thank You

Alexander Thomas



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