Ketamine to Facilitate Transition from Fentanyl to Buprenorphine: Theory and Application

Lucinda Grande, MD, FASAM
Tom Hutch, MD, FASAM
Andrew Herring, MD, FASAM

Presented at ASAM 54th Annual Conference, April 15, 2023
Ketamine to Facilitate Transition from Fentanyl to Buprenorphine: Theory and Application

Saturday April 15, 10:15-11:30

Lucinda Grande, MD, FASAM

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- Clinical Faculty, University of Washington School of Medicine
- Secretary/Treasurer, Washington Society of Addiction Medicine
- No Disclosures
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Tom Hutch, MD, FASAM

- Medical Director, We Care Daily Clinics
- Clinical Instructor, University of Washington School of Medicine
- No Disclosures
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Andrew Herring, MD

- Medical Director Substance Use Disorder Treatment, Alameda Health System
- No Disclosures
Learning Objectives

1. Describe the use of ketamine in anesthesia and off-label applications
2. Discuss the strategies, barriers and observations of clinical providers offering ketamine to treat and/or prevent buprenorphine-precipitated opioid withdrawal in the emergency department and outpatient settings
3. Discuss possible mechanisms of action of ketamine for managing buprenorphine-precipitated opioid withdrawal
Dr. Grande’s Overview

- Ketamine brief introduction
- The fentanyl challenge
- Ketamine-assisted buprenorphine induction: 21 cases
Ketamine
Ketamine Brief Introduction

- FDA approved 1970
- Dissociative anesthetic
- Minimal respiratory depression at anesthetic doses
- DEA Schedule III
Ketamine Off-Label Uses

- Procedural sedation
- Acute and Chronic Pain
- Treatment-resistant depression
- Non-medical (i.e. recreational)
Ketamine and Opioid Tolerance

- **Antagonist at the N-methyl-D-aspartate type glutamate receptor**
- **Activating the** NMDA receptor:
  - Allows development of opioid tolerance
- **Blocking the** NMDA receptor:
  - Reduces opioid tolerance

Trujillo et al., Science, 1991
Opioid-Sparing in Pain Management

Post-op Opioid Consumption

Systematic Review
70 Studies, 4,701 Patients

Standard difference in means and 95% CI

Favors Ketamine  Favors Placebo

-4.0  0.0  4.0

Laskowski et al., Can J Anesth, 2011
My Ketamine Experience

- Primary Care, 11 years
- 500+ ambulatory patients
- Chronic and acute pain, depression, suicidality*, other indications
- Oral / Sublingual Dosing
- Microdosing protocol**, 2-200+ mg/day total
- 145 prescribers, WA & OR***

Perceived Value in Chronic Pain

 Patients usually pay for the ketamine themselves, $50-75/month

Dose Ranges

Anesthesia (IV): 1-2 mg/kg/dose
Recreational (IM): 0.7-0.9 mg/kg/dose*
Infusion clinics (IV): 0.5 mg/kg/dose
Outpatient (SL): 0.01-0.1 mg/kg/dose**

Ketamine troches (lozenges)

*https://erowid.org/chemicals/ketamine/ketamine.shtml
**Based on 25% sublingual bioavailability, Peltoniemi; Clin Pharmacokinet 2016; DOI 10.1007/s40262-016-0383-6
My Buprenorphine Experience

- Primary Care, 11 years
- Low-barrier buprenorphine clinic, Medical Director 2019-2021
- 1500+ patients

Olympia Bupe Clinic pharmacy dispensing on-site
The Challenge

Deaths per 100,000 Standard Population

CDC, NCHS Data Brief No. 394, December 2020
The Challenge

Precipitated Opioid Withdrawal

“Suboxone does not work with fentanyl.”

“Everything is not right anymore”:
Buprenorphine experiences in an era of illicit fentanyl.
Silverstein et al., International Journal of Drug Policy 74 (2019) 76-83
Induction Strategies

- Low Dose Induction
- High Dose Induction
- QuickStart: Naloxone-Assisted Induction

Chen et al., (2021) Rutgers ECHO "Alternative Buprenorphine Induction Strategies"

CASE REPORT

Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient With Fentanyl Use

Christian Hailozian, BS, Joshua Luftig, PA, Amy Liang, MD, Melena Outhay, MD, Monish Ullal, MD, Erik S. Anderson, MD, Mariah Kalmin, PhD, Steve Shoptaw, PhD, Mark K. Greenwald, PhD, and Andrew A. Herring, MD
Eureka!
Ketamine-Assisted Induction - Outpatient

Buprenorphine 0.25-16 mg/day

2mg/0.5mg

4 mg + 16 mg

Ketamine 4–16 mg PRN

Buprenorphine (8-32 mg/day)
Case 1: Low Dose Induction Withdrawal Relief

- 26 year old female smoking fentanyl 10 times daily x 6 months
- Rx: Buprenorphine flexible upward taper + clonidine, gabapentin, ketamine
- Day 1: BUP 0.5 mg x 4, then 1 mg: Mild withdrawal
- Day 2: BUP 4 mg:
  - **Severe withdrawal:** restlessness, pain in abdomen, back and joints, a creepy-crawly sensation, furrowed brow, feeling of heavy weight. Lay in bed moaning for 18 hours.
  - **KET 4 mg:** After 5 minutes, complete resolution of symptoms. She was up walking. Her voice was cheerful and her furrowed brow relaxed.
Case 1: Low Dose Induction Withdrawal Relief

**Days 3-4:**
- KET 4-16 mg several times daily, pain relief
- BUP 2-4 mg several times daily

**Day 5:**
- On awakening, felt cheerful and optimistic. Felt no need for any medication. Took BUP 8 mg as directed.

**Total for days 1 through 4:** KET 64 mg, BUP 24 mg

**Lost to follow-up**
Case 2: High Dose Induction Withdrawal Relief

- 25 year old female, fentanyl 20 tablets daily
- Rx BUP 16-32 mg, plus chlordiazepoxide 25 mg BID x 7 days and KET 16 mg x 4
- Day 1: BUP 16 mg: severe withdrawal
  - KET 4 mg had minimal effect; an additional 8 mg provided relief
- Days 2-7: intermittent use of KET 8 mg provided relief from withdrawal symptoms and improved her mood
- Follow-up: Stable on BUP 16-24 mg/day after 3 weeks
Case 3: Low Dose Induction
Withdrawal Relief and Prevention

🌟 38 year old male, recent use of fentanyl
🌟 Rx: BUP 7 day upward taper 0.25-16 mg/day, clonidine, gabapentin, KET
🌟 At OTP: methadone downward taper starting at 30 mg
🌟 “For a few days”: BUP and KET 4 mg together: mild withdrawal symptoms
🌟 One day, buprenorphine without ketamine: severe withdrawal. KET 8 mg "took the edge off."
🌟 Followup: Stable on BUP 20 mg/day after 4 weeks
Case 4: High Dose Induction
Withdrawal Prevention

- 27 year old female, fentanyl 6 times/day x 8 months
- Day 0: last fentanyl use. 2 hours later: BUP 0.5 mg
- Day 1: BUP 4 mg BID, KET 8 mg before each dose
  - No withdrawal. Mild sweats/chills
- Day 2: BUP 4 mg 6 times, KET 8 mg before each dose
  - No withdrawal. Mild sweats/chills
  - Test of fentanyl: no rewarding effect
- **Day 3: Happy, excited.** Wants to “go to the park, get the oil changed, regular things.” 4 year old daughter is happier, can tell that mom is getting better.
Case 5: Problematic Induction

- 52 year old male, fentanyl 30-40 pills/day, cocaine & beer daily
- 1 hour after last fentanyl use: KET 16 mg, BUP 8 mg (swallowed)
- 1 hour later: Horrible withdrawal
- First 2 hours: total KET 48 mg, BUP 24 mg, clonidine 0.2 mg, gabapentin 600 mg
- No improvement in w/d sx, frightening dissociation
- Finally fell asleep
- Follow-up: stable on BUP 16 mg/day
Case 5: Problematic Induction
Unique Features, Learning Points

- Older, higher baseline fentanyl use, daily cocaine, swallowed BUP
  - Implications unclear
- First BUP only 1 hour after fentanyl
  - Wait 12+ hours after fentanyl before BUP
  - Use KET as needed while waiting
- Total KET 48 mg in 2 hours
  - Limit KET to 32 mg in 8 hours
16 Additional Patients

☀ Successes:
☀ KET 4-16 mg reliably provides withdrawal relief or prevention of precipitated withdrawal

☀ Challenges:
☀ Phone contact inconsistent
☀ Some don’t pick up ketamine
☀ Some lost to followup
Additional Learning Points

- Also works for methadone to BUP transition
- Less KET required for prevention than relief?
Current Protocol

☀ Close monitoring by phone (more than once daily if possible)

☀ First 12 hours after last fentanyl use:
  ☀ KET 8 mg when starting to feel uncomfortable
  ☀ Max KET 32 mg within any 8 hour period
Current Protocol

After 12-24 hours, and uncomfortable withdrawal:

- Once: KET 16 mg + BUP 4 mg
- THEN Q4 hours: KET 8 mg + BUP 4 mg

Goal BUP 16-24 mg in first 24 hours

Max KET 32 mg within any 8 hour period
If things don’t go well …

KET helps, but we continue to seek a reliable protocol for a smooth and quick transition.

Options:

- More KET (8 mg Q15-30 minutes x 3)
- More BUP (8 mg Q15-30 minutes x 3)
- Clonidine, gabapentin, etc.
- All of the above?
- Inpatient setting: could use benzos
Addiction Clinics Use Club Drug to Save Lives

Ketamine troches (lozenges)

August 2024
Dr. Herring
Don’t believe the hype

Emergency Departments are a beautiful triumph of democracy

• Crowding and costs are manufactured by non-clinical factors
• Free, 24-7
• Comprehensive—medicine, food, shelter
• Ketamine is cheap, easy, and every ER doc knows how to use it
Integrated systems of care should be standard

Emergency Department
24-7 partner to fill in treatment gaps and apply high-intensity treatments
Ketamine is an obvious intervention

- 3159 participants
- Enhanced mood
- Reduced pain

Brief Report

Effective analgesia with low-dose ketamine and reduced dose hydromorphone in patients with severe pain

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Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain

Terence L. Ahern MD a,b, Andrew A. Herring MD b, Michael B. Stone MD b, Bradley W. Frazee MD a,c

Methods. We prospectively administered 15 mg intravenous ketamine followed immediately by continuous ketamine infusion at 20 mg/h for 1 hour. Optional morphine (4 mg) was offered at 20, 40, and 60 minutes. Pain intensity, vital signs, level of sedation, and adverse reactions were assessed for 120 minutes.

Correspondence

Emerging applications of low-dose ketamine for pain management in the ED

Patients undergoing brief painful procedures, (2) patients with chronic pain on high-dose opioids presenting with patients in whom pain
Opioid induced pain = withdrawal
Weak direct agonism

Strong inhibition of tolerance = potentiation
Sustained mood elevation with a single dose of ketamine

☀️ ketamine can produce rapid onset and sustained (>2 weeks) antidepressant effects after a single-dose

Hashimoto K. Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. Biochem Pharm. 2020;177:113935.

Ketamine is very safe
How to use ketamine

- Total of 0.5 mg / kg is a good target for lasting effects
- 40mg IV over an hour
- 20mg IV over 15-20 x 2

The slower the infusion the lower the risk of fear and confusion.

Motivational interviewing promotes placebo and enjoyment
When to Use Ketamine

🌟 Preemptively in patients with risk for depressive symptoms and low motivation
  🌟 i.e. everyone starting buprenorphine

🌟 Symptom targeted
  🌟 Pain
  🌟 Precipitated withdrawal
  🌟 Depression
HR 125, BP 170/90, 10/10 pain, vomiting, “feels terrible”

Case

Strong dose of buprenorphine too early in withdrawal + Patient sensitivity

Treatment Is more bup

For refractory withdrawal ketamine fentanyl

Opioid balance

Rapidly generated withdrawal State

Treatment of precipitated withdrawal:
Administer additional 16 mg SL bup immediately
Reassess in 30-60 minutes, if continued distress remains: Repeat 8-16 mg bup SL

For intractable withdrawal:
May consider alpha-2 agonists (clonidine or dexmedetomidine), antipsychotics (e.g. haloperidol), cautious use of benzodiazepines (i.e 1-2 mg PO lorazepam x 1), high potency opioid (e.g. fentanyl 100-200mcg IV q30 or infusion), ketamine (0.3 mg/kg IV slow push q50 minutes or continuous infusion until calm)

Withdrawal is managed, continue daily bup dose
Dr. Hutch
Clinical Implementation
Clinical Implementation

- Most patients start buprenorphine via outpatient clinics or OTPs (not hospitals or EDs)
- Ketamine not available for outpatient prescription at most retail pharmacies
- How can we connect outpatients with safe and appropriate ketamine formulations?
Clinical Implementation - Overview

Prescribing
Access
Encounter
Follow-up
Clinical Implementation - Overview

The Regulatory Sea of Troubles

Off-Label Prescribing

FDA Approval

Separate Registration

Part 2 ROI

Diversion Concerns

Pharmacy Commission

Insurance Coverage

503A Pharmacies

Chain of Custody

21 C.F.R.

DEA 5% Rule

Safe Storage

Stigma

DEA Black Bag Rule

Risk Management Departments

Recordkeeping

Teleprescriptions of Scheduled Meds

Medical Commission

Expensive Vaults

The Ghost of Harry Anslinger

"White-Bagging"

Vaults

DEA 5% Rule

ROI
Is this legal to prescribe?

- Schedule III
- Any DEA-licensed prescriber
- Off-label prescribing is legal and common
  - ~1 in 5 of all drug prescriptions in US are off-label
- This use of ketamine is supported by both theory and clinical evidence

Clinical Implementation – Prescribing

🌟 Off-label prescribing “is a matter of medical judgment” and FDA does not regulate medical practice*

🌟 Although not required, † informed consent about off-label use is advised

🌟 Helpful to network with others doing this
  - Regular case conference series, provider networks

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*Bax Global Inc v Brenneman, Ohio 695 (Ohio Ct App 2007)

†Canterbury v Spence, 464 F2d 772 (DC Cir 1972)
Clinical Implementation - Prescribing

☼ Potential prescriber models for ketamine Rx
☼ The prescriber of the buprenorphine
☼ A specialized prescriber in the clinic
☼ An outside consultant, via referral
Clinical Implementation - Prescribing

🌟 Telemedicine Rx of Schedule III controlled substances

🌟 Ryan Haight Online Pharmacy Consumer Protection Act
  - Requires exam before controlled Rx
  - Exceptions:
    - Patient is located at a clinic or hospital for visit
    - Patient has been examined by another DEA-licensed practitioner

21 U.S.C. 802(54)(A)–(G)
Non-public health emergency-related exceptions to the Ryan Haight OPCPA of 2008
Clinical Implementation - Prescribing

- DEA Notice of Proposed Rulemaking, March 2023
- Could allow for less than 30 days of ketamine to be prescribed via telemedicine without physical evaluation

“Telemedicine Prescribing of Controlled Substances When the Practitioner and the Patient Have Not Had a Prior In-Person Medical Evaluation,” Federal Register 88 FR 12875, 3/1/2023
Clinical Implementation - Access
Clinical Implementation - Access

Prescribing for unobserved use
- Compounded forms (troche, syrup, etc.)
- Compounding pharmacies
  - 503A vs 503B
  - On-site storage

Dispensing/administration
- Stock forms (IV, IM)

Clinical Implementation - Access

☀ Compounding pharmacy
  ☀ We found a nearby pharmacy willing to collaborate
  ☀ Made a batch of 16 mg troches to keep cost down
  ☀ 4 troches/package for $10/package
  ☀ Labeled for specific patient when dispensed
Clinical Implementation - Access

**Cost**
- 50 patients: $500

**Funding**
- Insurance – very unlikely
- Patient payment – barrier, avoiding this
- Clinic funds
- Small grant
- Contribution from pharmacy
Clinical Implementation - Access

🌟 Compounding pharmacy considerations
🌟 Can patient receive ketamine, buprenorphine, and comfort medications at same pharmacy?
🌟 Does compounding pharmacy bill Medicaid?
🌟 Do pharmacy and clinic hours line up?
Clinical Implementation – Access

🌟 Scenario 1: Patient goes to pharmacy

🌟 Patient has a ride or a vehicle, or;
🌟 Clinic provides travel voucher, or;
🌟 Clinic staff member drives patient
Clinical Implementation – Access

 Scenario 2: Pharmacy delivers ketamine to patient

 - Courier – but patient must be at a predictable nearby location
 - US Priority Mail
  - Patient needs a reliable mailing address, be able to sign for package
  - Delays ketamine start
Clinical Implementation – Access

 Scenario 3: Compounding pharmacy delivers ketamine to clinic

“White bagging:” distribution of patient-specific medication from a pharmacy to a clinic for distribution or administration

Most state pharmacy commissions discourage this, as does our local DEA office

OTPs can’t receive or dispense controlled medications not specifically FDA-approved as MOUD

Clinical Implementation - Encounter

- Identify candidates for ketamine-assisted buprenorphine induction

- WCDC inclusion criteria:
  - Under 60 years old
  - No severe medical comorbidities
  - English-speaking, with a phone and ability to follow-up
  - Reasonable shelter and ability to keep medication safe
  - Regular fentanyl use for at least a few months
Medical practitioner presents option

“There is a medication called ketamine that may reduce or prevent the painful withdrawal symptoms that can occur during the transition onto buprenorphine. It is not FDA approved for this purpose, but it has been in wide use since the 1970s for other purposes including as a pain medicine. If you are interested, I can refer you to a local doctor who can prescribe it for you.”
Clinical Implementation – Encounter

- Patient signs ROI for ketamine consultant
- Medical practitioner:
  - Texts/emails consultant with basic info
  - Prescribes buprenorphine & comfort meds
- Medical assistant: scans & faxes ROI with clinic note
- Ketamine consultant: telemedicine visit, reviews history, counsels, Rx ketamine to pharmacy
Clinical Implementation – Follow-up

- Medical provider and/or consultant calls daily or near-daily
- Therapeutic value to daily contact
- If induction protocol is long, daily calls may be difficult, especially at a large scale
Clinical Implementation – Alternate Logistics

- Hospital-affiliated clinics
- Ketamine solution could be administered with buprenorphine in clinic
Clinical Implementation – Diversion Risk

- Total ketamine dispensed: 64 mg (16 mg, #4)
- Minimal street value
- Very low risk, even if taken all at once
  - Mild dissociation for 15-30 minutes
- Consider risk-benefit ratio
Final Takeaways/Summary

☀ Ketamine is FDA approved for anesthesia, but can be used off-label to treat acute and chronic pain and depression.

☀ Ultra-low dose ketamine ("microdosing") can both relieve and prevent opioid withdrawal symptoms during buprenorphine induction from fentanyl.

☀ Implementing ketamine-assisted buprenorphine induction may be challenging for clinics, but determination and creativity can overcome barriers.
References, Dr. Grande

- CDC, NCHS Data Brief No. 394, December 2020
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