# 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

# Disclosure Information

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

Saturday April 15, 10:15-11:30

Lucinda Grande, MD, FASAM

- Partner, Pioneer Family Practice, Lacey WA
- 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

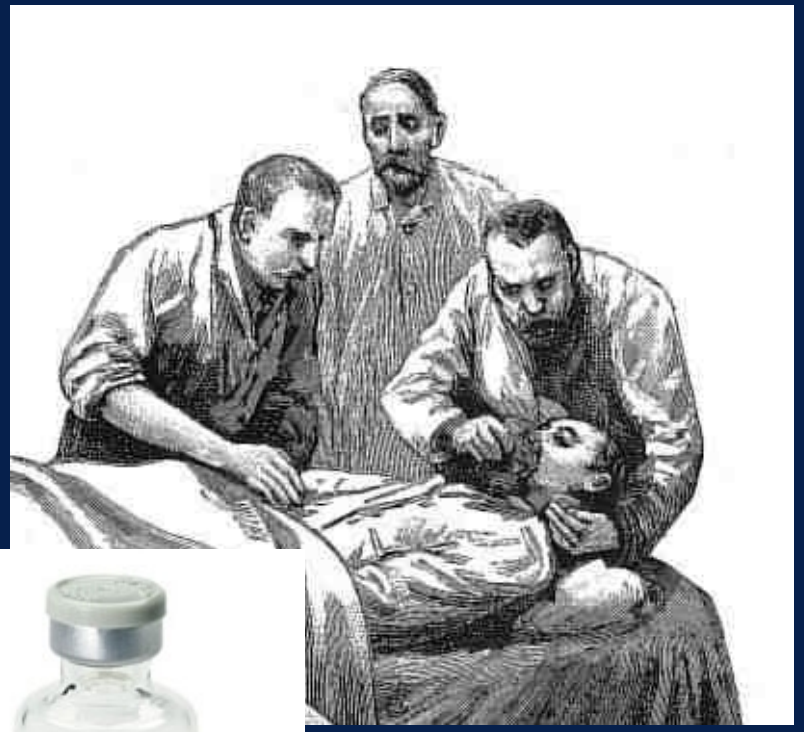
# Learning Objectives

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 HCl
INJECTION, USP
FOR SLOW IV OR IM USE
500 mg/10 mL*
(50 mg/mL)
Rx ONLY

# 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)

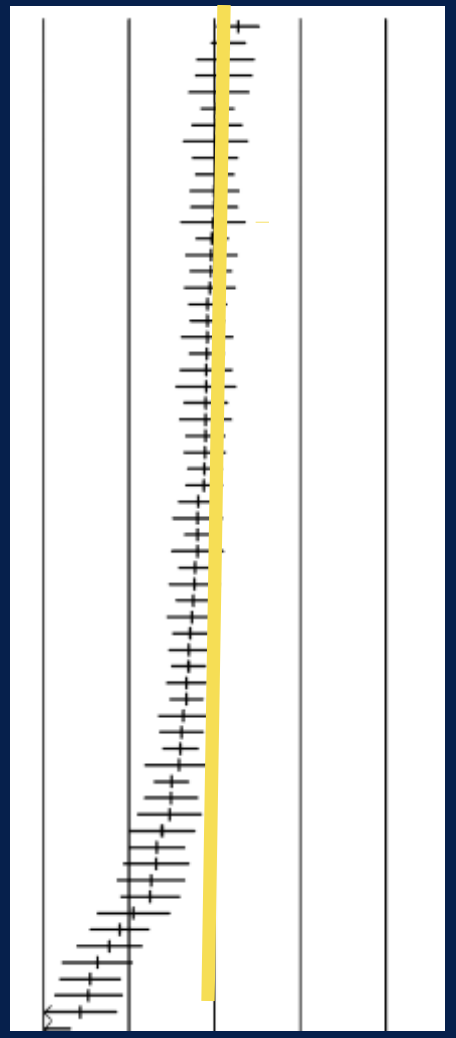
"Ketamine: Drug Information." ©2023, UpToDate

# 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



-4.0 0.0 4.0

Favors Ketamine Favors Placebo

## Post-op Opioid Consumption

Systematic Review
70 Studies, 4,701 Patients

Standard difference in means and 95% CI

Laskowski et al., Can J Anesth, 2011

# My Ketamine Experience

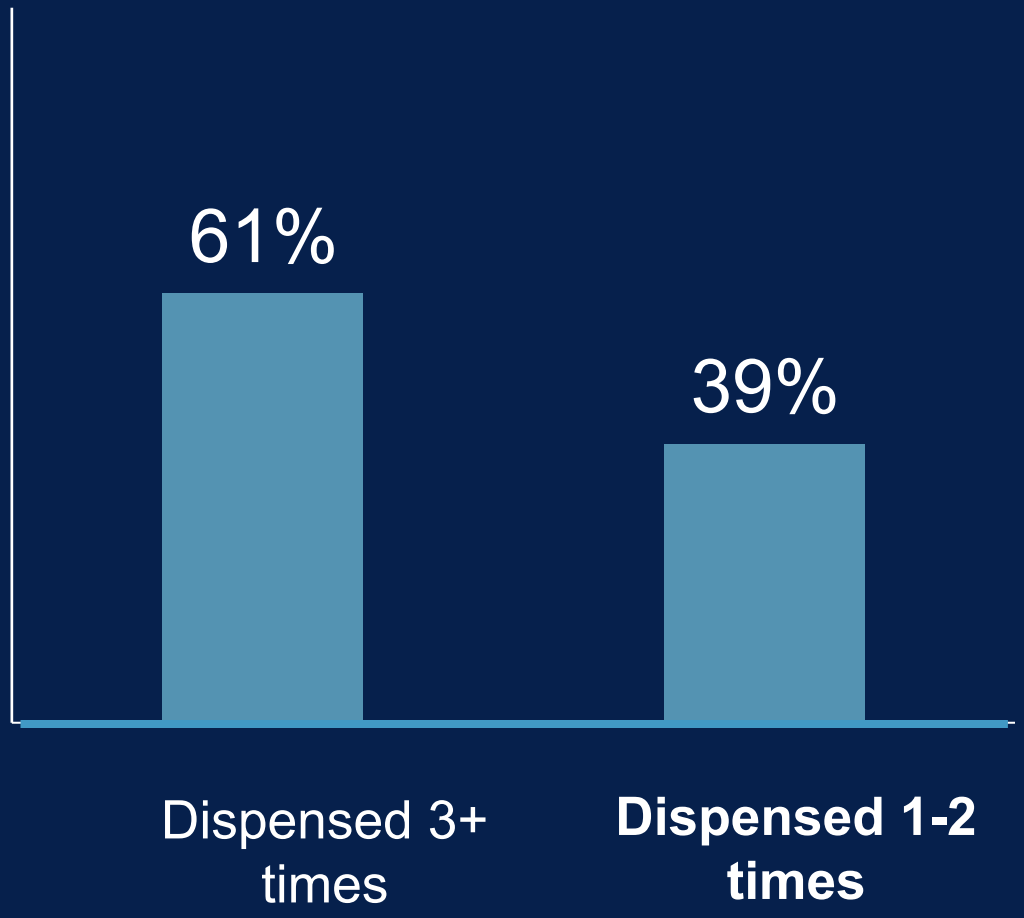
- Primary Care, 11 years
- 500+ ambulatory patients
- Chronic and acute pain, depression, suicidality*, other indications
- Oral / Sublingual Dosing
- Microdosing protocol**, 2-200+ mg/day total
- 145 prescribers, WA & OR***

*Grande-LA, Prim Care Companion CNS Disord 2017.

**Grande-LA, Protocol for New Prescribers, 2018, Copyright 2023.

***Grande (2023) Analysis of ketamine prescription data from Peninsula Compounding Pharmacy, 2023 (unpublished).

# Perceived Value in Chronic Pain



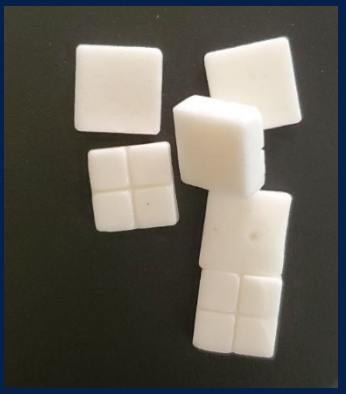

N=240
P<0.002

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

Grande et al. Retrospective Analysis (unpublished, 2017)

# 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

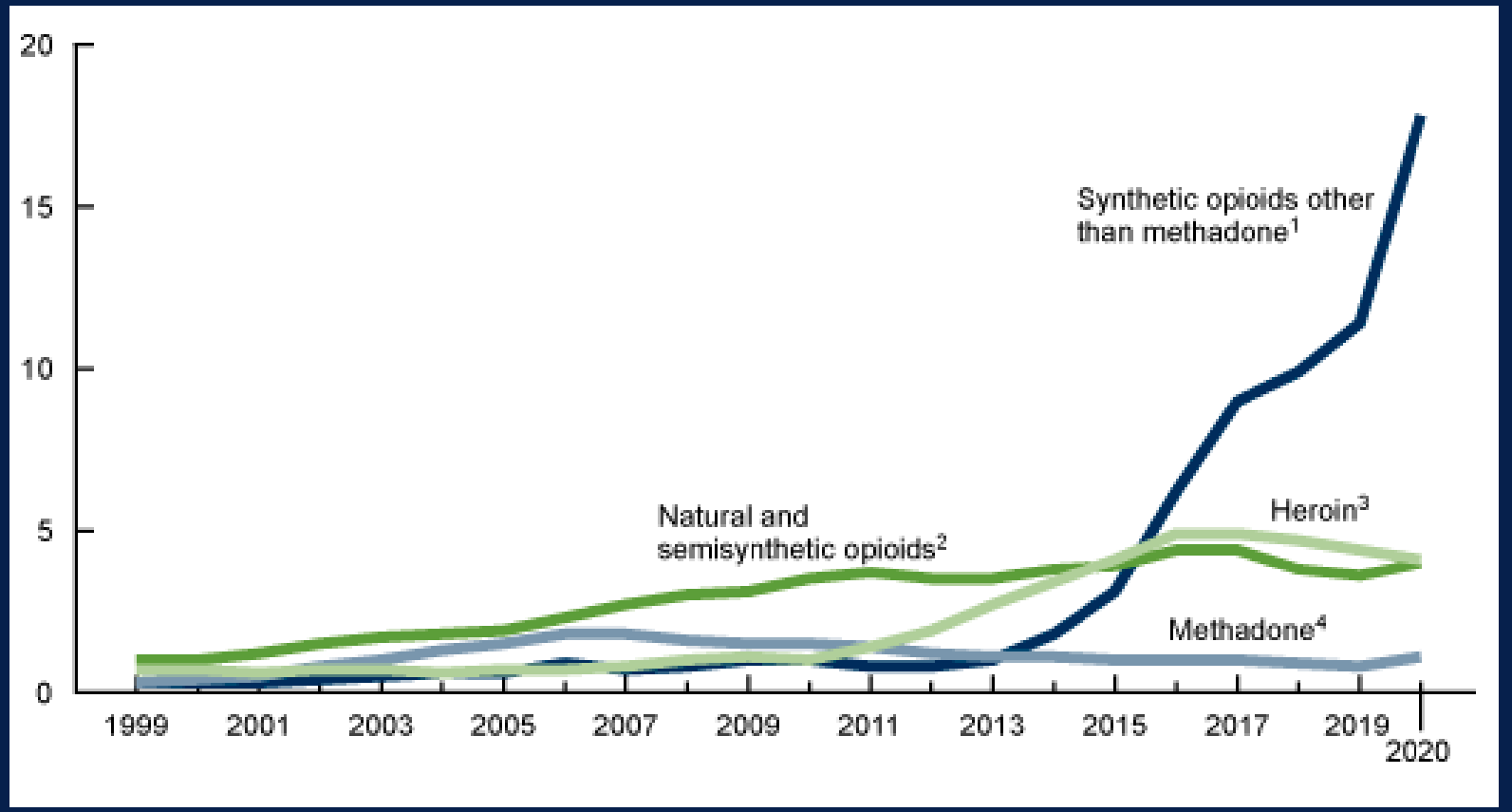
# My Buprenorphine Experience

- 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

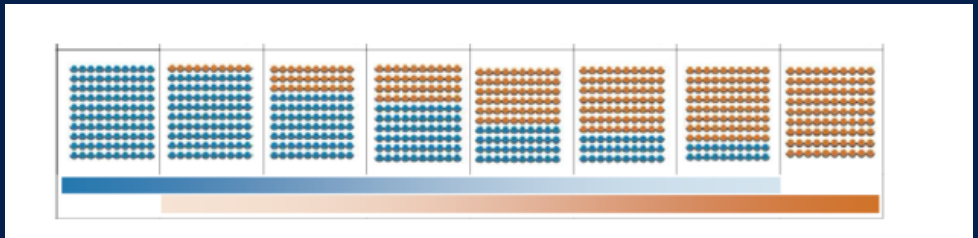
## Precipitated Opioid Withdrawal

"Suboxone *does not work* with fentanyl."

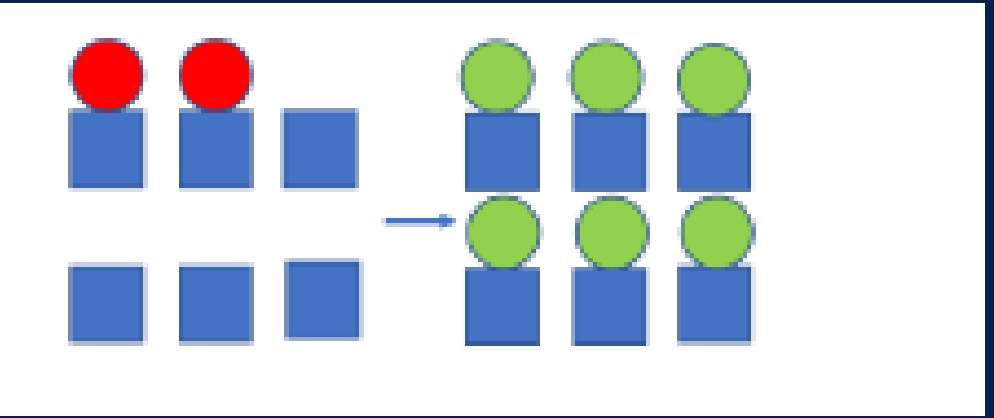
**"Everything is not right anymore":**
**Buprenorphine experiences in an era of illicit fentanyl.**
Silverstein et al., International Journal of Drug Policy 74 (2019) 76-83

# Induction Strategies

- Low Dose Induction



- High Dose Induction



- QuickStart: Naloxone-Assisted Induction

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

Randall et al., J Addict Med, 2023 Mar-Apr 01;17(2):237-240.

# Ketamine-Assisted Induction - ED

CASE REPORT

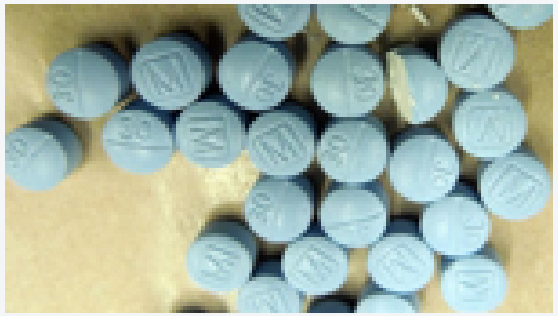
## Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient With Fentanyl Use

*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*

Hailozian et al., J Addict Med 2022 Jul-Aug;16(4):483-487

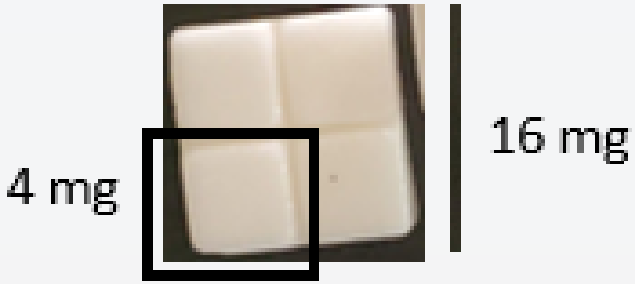
# Eureka!

# Ketamine-Assisted Induction - Outpatient



Buprenorphine 0.25-16 mg/day


+




Ketamine 4–16 mg PRN


Buprenorphine (8-32 mg/day)

Grande et al., Poster at California Society of Addiction Medicine, 2022

# 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 …

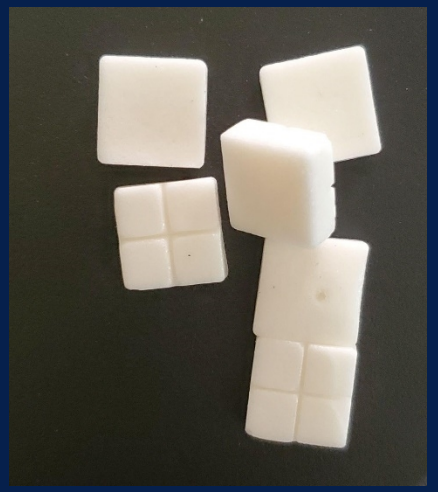
- KET helps, but we continue to seek a reliable protocol for a smooth and quick transition.
- Options:
  - More KET (8 mg Q15-30 minutes x 3)
  - More BUP (8 mg Q15-30 minutes x 3)
  - Clonidine, gabapentin, etc.
  - All of the above?
  - Inpatient setting: could use benzos

August 2024

U.S. INTERNATIONAL CANADA ESPAÑOL 中文

The New York Times

# *Addiction Clinics Use Club Drug to Save Lives*



Ketamine troches (lozenges)

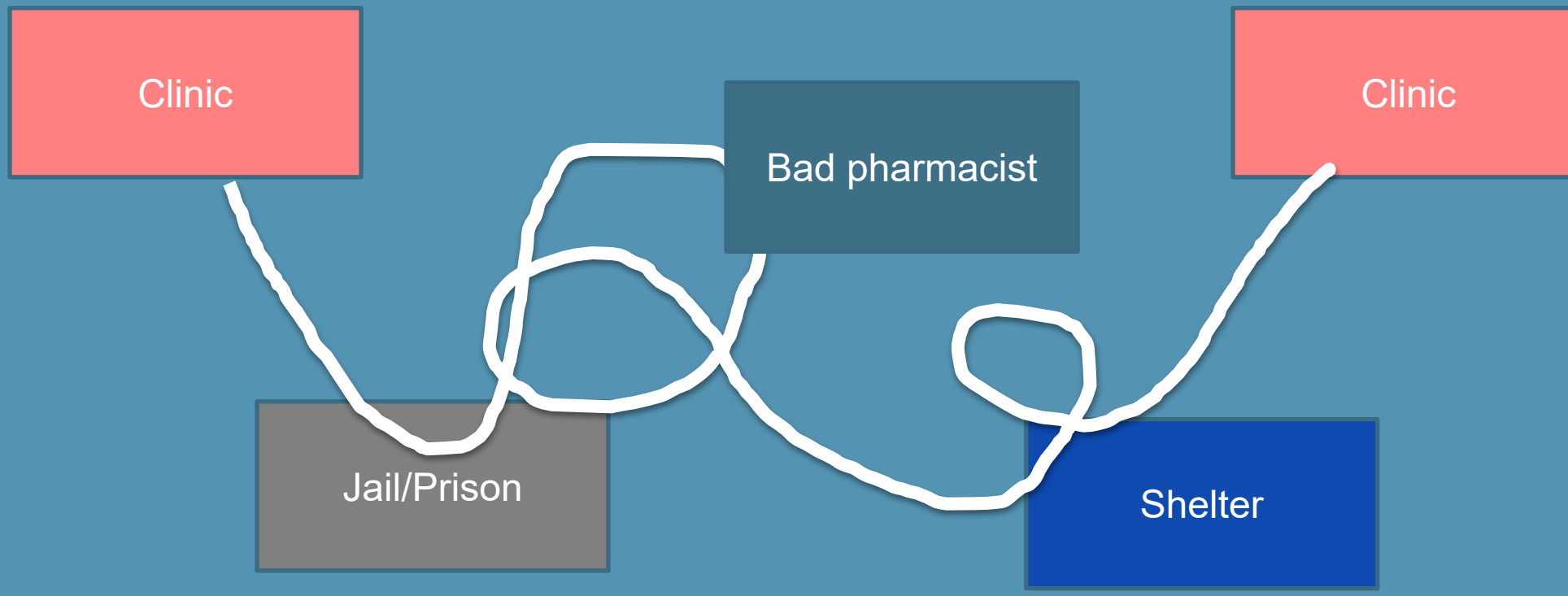
# Dr. Herring

# 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

Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN

Check for updates

## Efficacy and safety of perioperative application of ketamine on postoperative depression: A meta-analysis of randomized controlled studies

Jie Guo[1,5], Di Qiu[2,5], Han-wen Gu[2], Xing-ming Wang[2,3], Kenji Hashimoto[3✉], Guang-fen Zhang[4✉] and Jian-jun Yang[2✉]



Guo, J., Qiu, D., Gu, Hw. *et al.* Efficacy and safety of perioperative application of ketamine on postoperative depression: A meta-analysis of randomized controlled studies. *Mol Psychiatry* (2023). https://doi.org/10.1038/s41380-023-01945-z



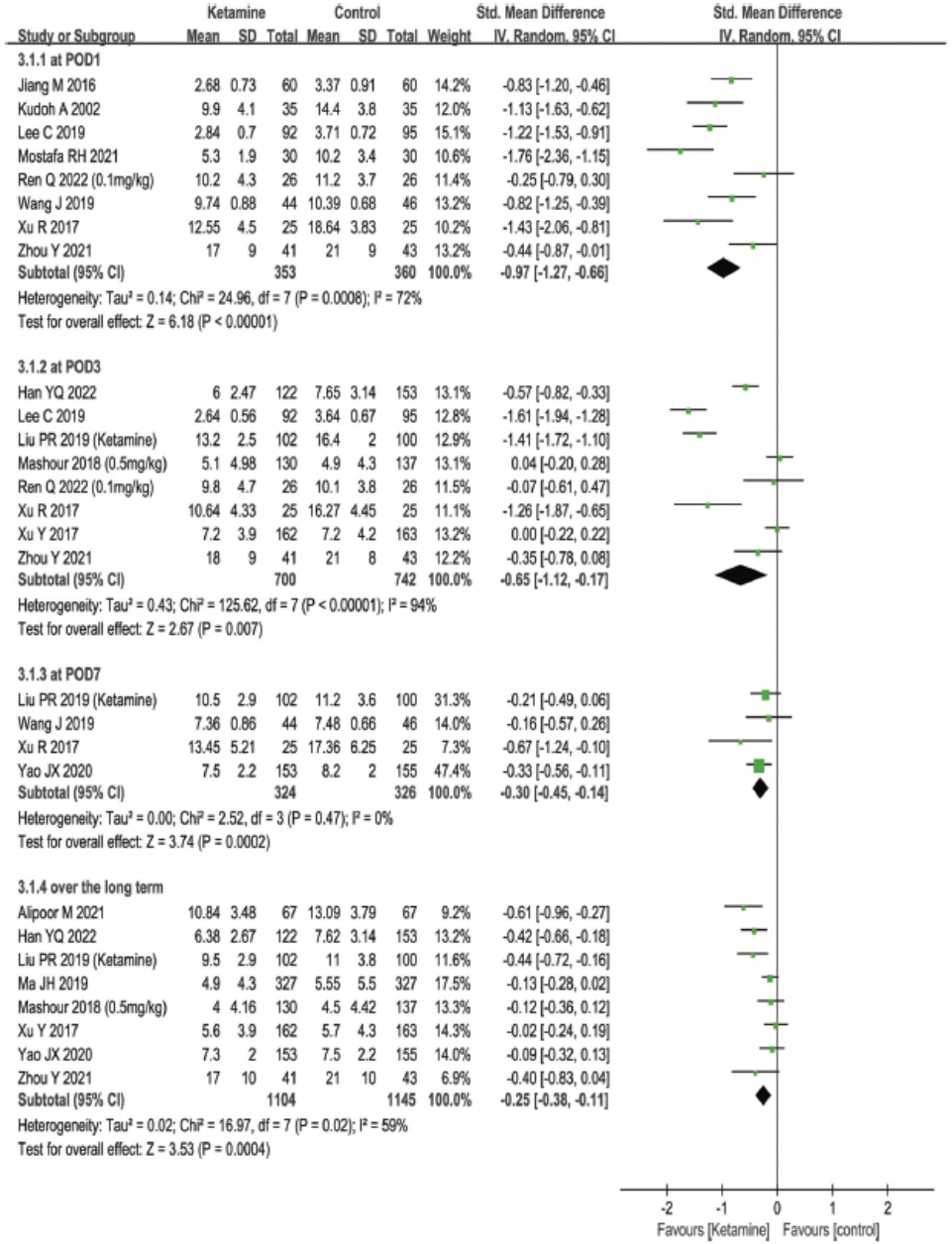



**Fig. 3 The effects of perioperative application of ketamine on postoperative depression.** Forest plots of the postoperative depression rating scale in randomized controlled trials. Random-effects meta-analysis. POD postoperative day. CI confidence interval. df degrees of freedom.

# Ketamine WORKS

American Journal of Emergency Medicine 31 (2013) 847–851

Contents lists available at SciVerse ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Brief Report

## Effective analgesia with low-dose ketamine and reduced dose hydromorphone i patients with severe pain☆,☆☆

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

[a] Department of Emergency Medicine, Alameda County Medical Center, Highland Hospital, Oakland, CA, USA
[b] Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA
[c] De

Pain Medicine

Pain Medicine 2015; 00: 00–00
Wiley Periodicals, Inc.

***Brief Research Report***

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

**Terence L. Ahern MD,* Andrew A. Herring MD,*,† Steve Miller MD,* and Bradley W. Frazee MD*,†**

*Departments of Emergency Medicine, Alameda Health System, Highland Hospital, Oakland; †Emergency Medicine, University of California, San Francisco, California, USA

**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, vitals signs, level of sedation, and adverse reactions were assessed for 120 minutes.**

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contributions

## The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED☆,☆☆,★,★★

Terence L. Ahern, MD [a,*], Andrew A. Herring, MD [a,b], Erik S. Anderson, MD [a], Virat A. Madia, MD [a], Jahan Fahimi, MD [a,b], Bradley W. Frazee, MD [a,b]

[a] Department of Emergency Medicine, Alameda Health System, Highland Hospital, Oakland CA
[b] Department of Emergency Medicine, University of California, San Francisco, San Francisco CA

American Journal of Emergency Medicine (2012) xx, xxx–xxx

ELSEVIER

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

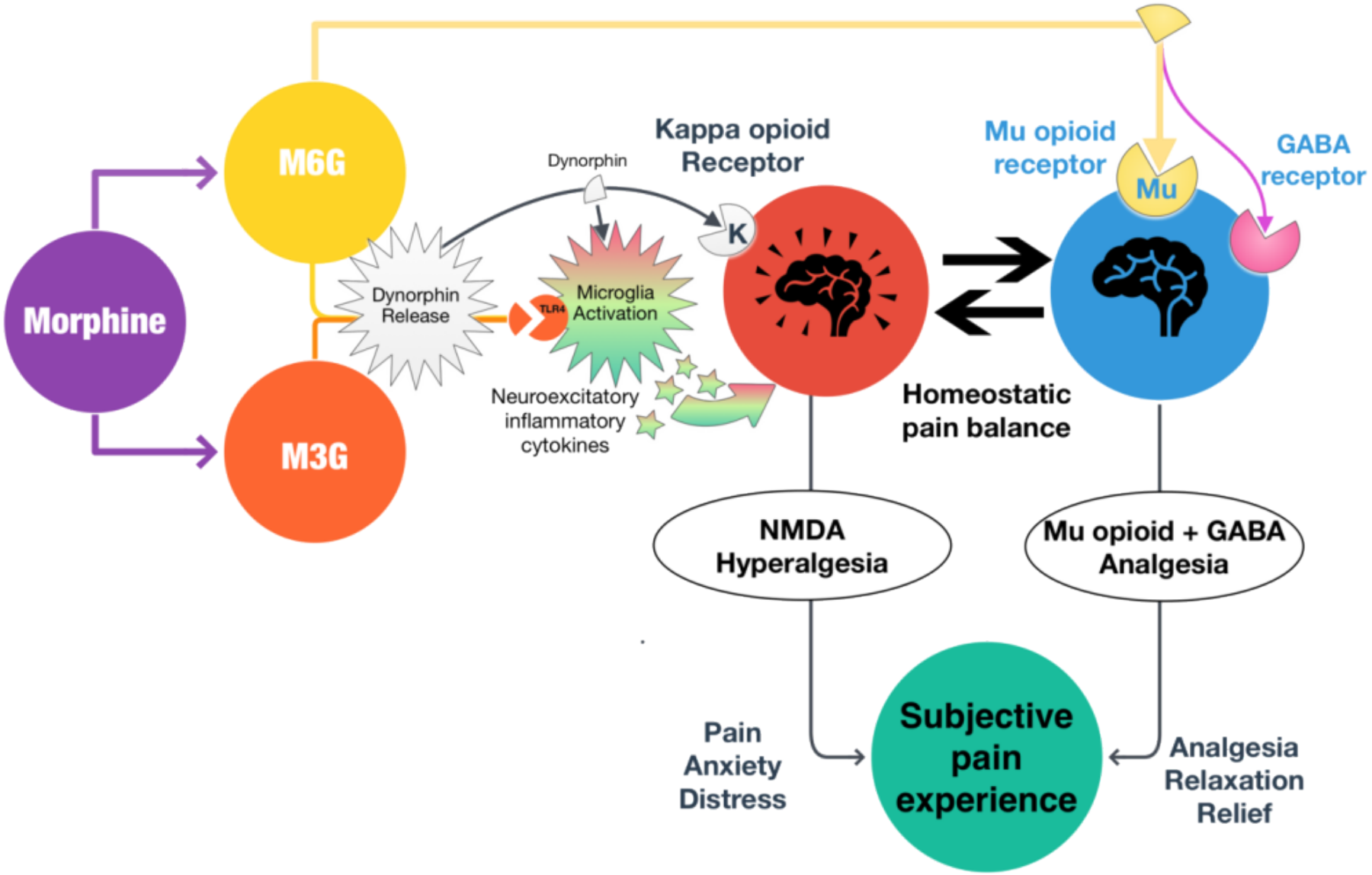
**Correspondence**

**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

HIGHLAND EMERGENCY
DEPARTMENT OF EMERGENCY MEDICINE
ALAMEDA HEALTH SYSTEM - HIGHLAND HOSPITAL

# Opioid induced pain=withdrawal



biomolecules

MDPI

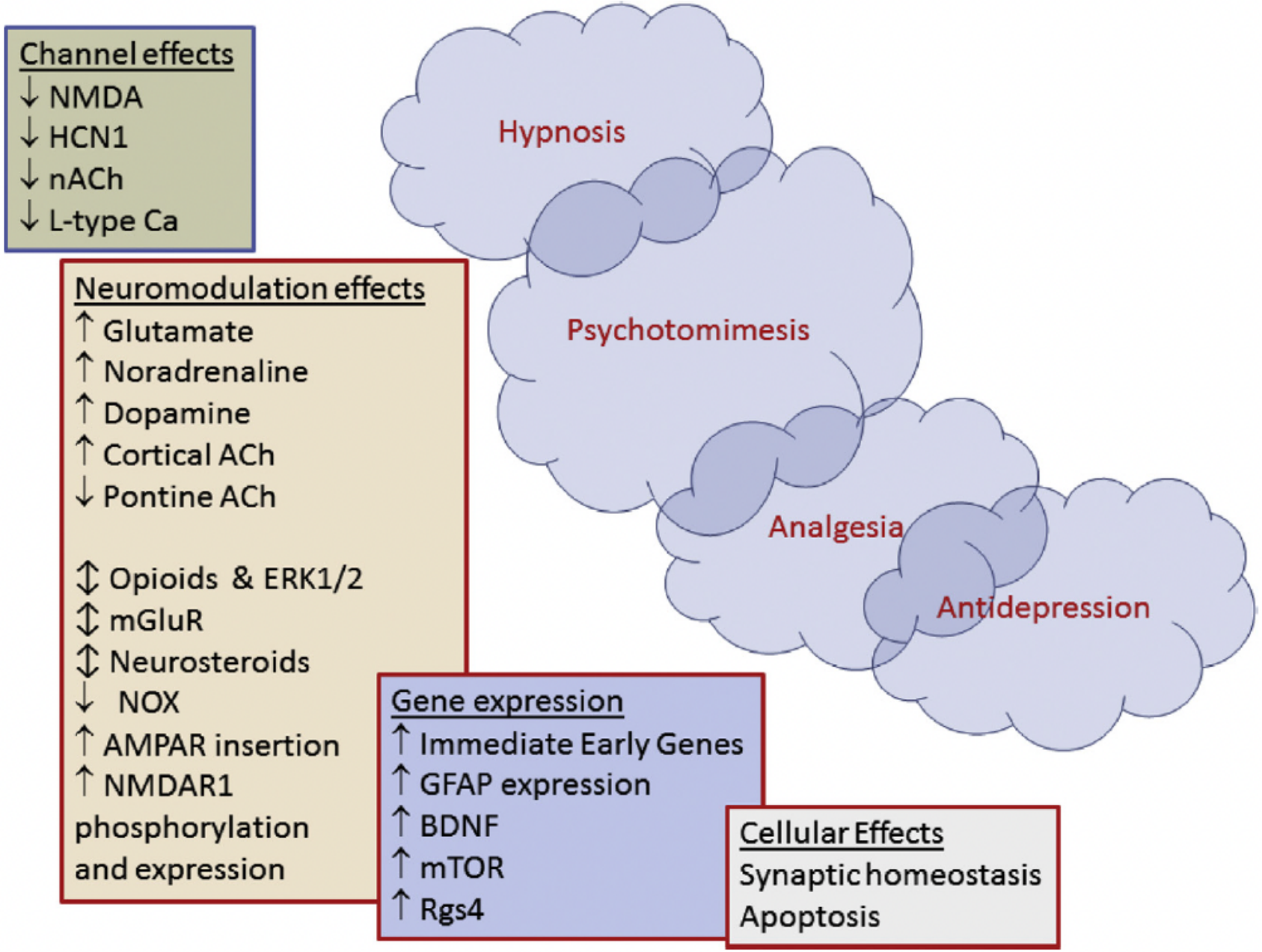
Article

**Ketamine Improves Desensitization of μ-Opioid Receptors Induced by Repeated Treatment with Fentanyl but Not with Morphine**

Yusuke Mizobuchi [1,2,3], Kanako Miyano [2], Sei Manabe [4], Eiko Uezono [2,5], Akane Komatsu [5], Yui Kuroda [5], Miki Nonaka [2], Yoshikazu Matsuoka [4], Tetsufumi Sato [3], Yasuhito Uezono [2,6,*] and Hiroshi Morimatsu [1,4]

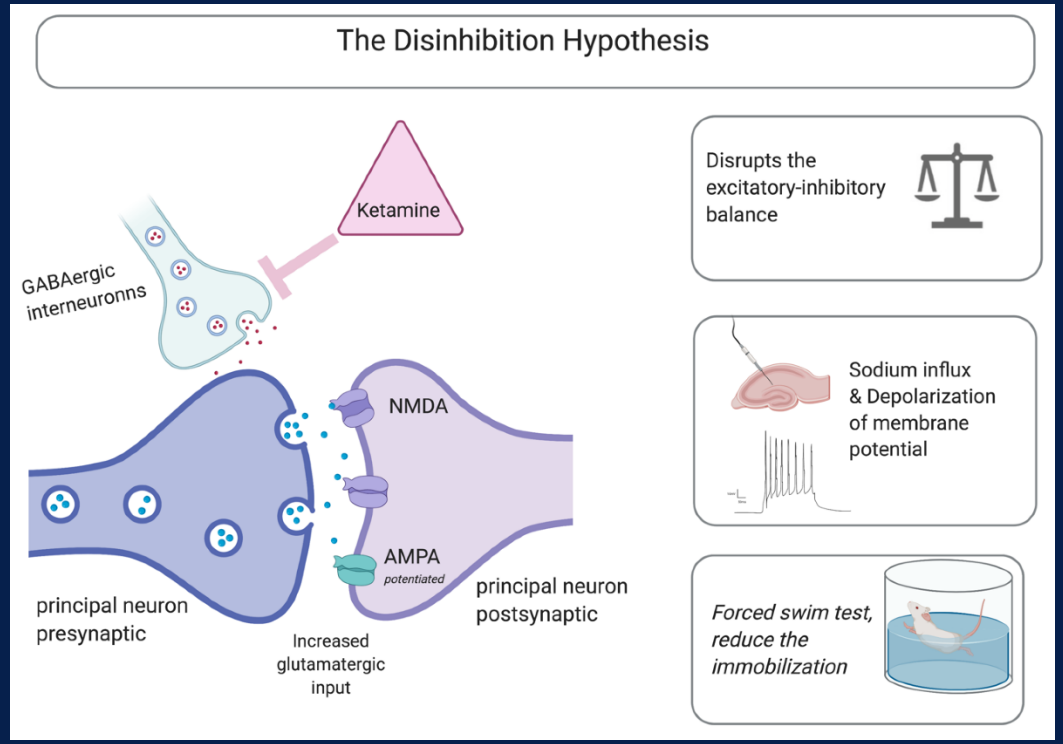
- Weak direct agonism
- Strong inhibition of tolerance = potentiation





# Sustained mood elevation with a single dose of ketamine

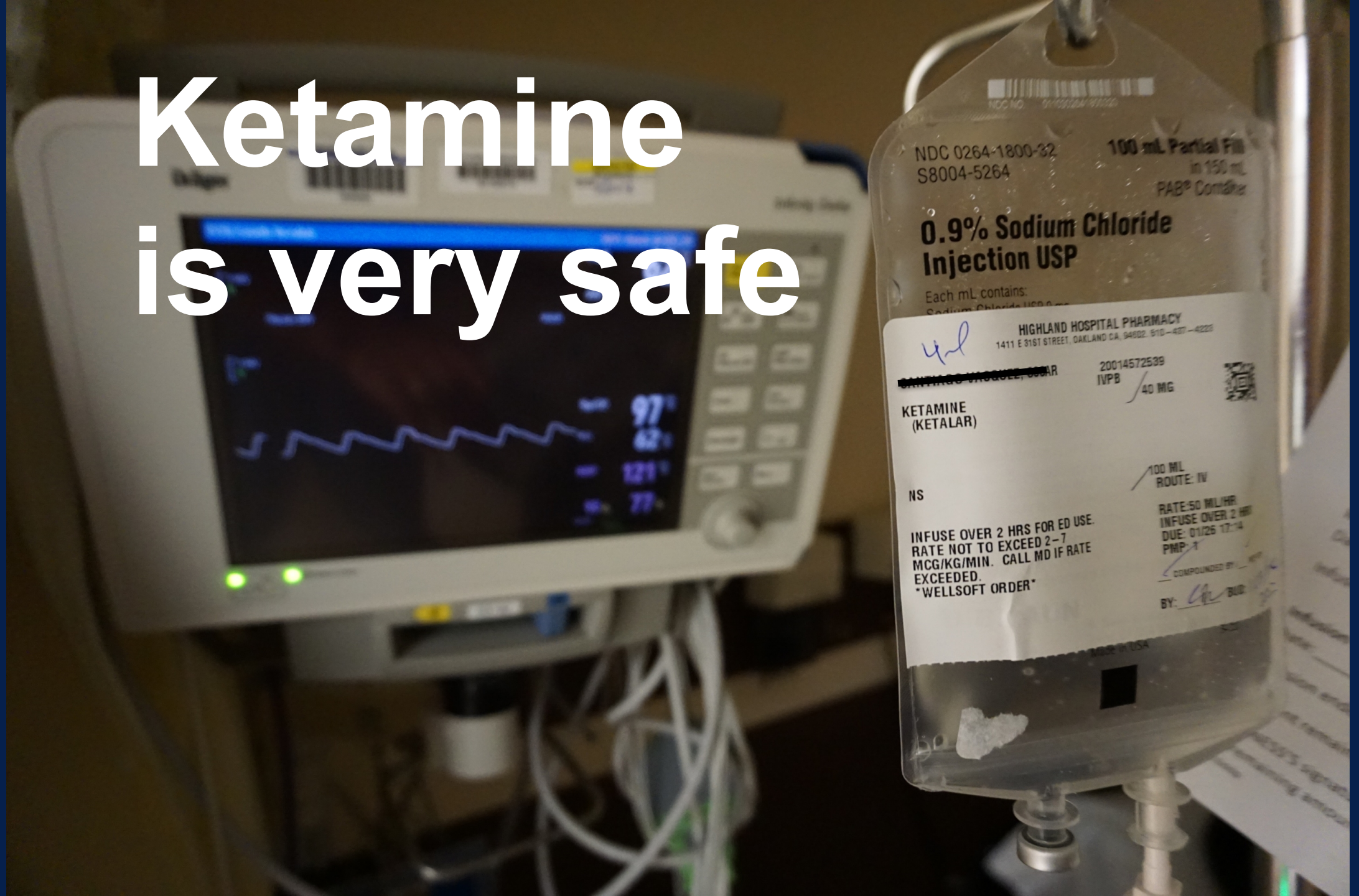
- ketamine can produce rapid onset and sustained (>2 weeks) antidepressant effects after a single-dose




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

43. Hashimoto K. Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. Psychiatry Clin Neurosci. 2019;73:613–27.

# Ketamine is very safe

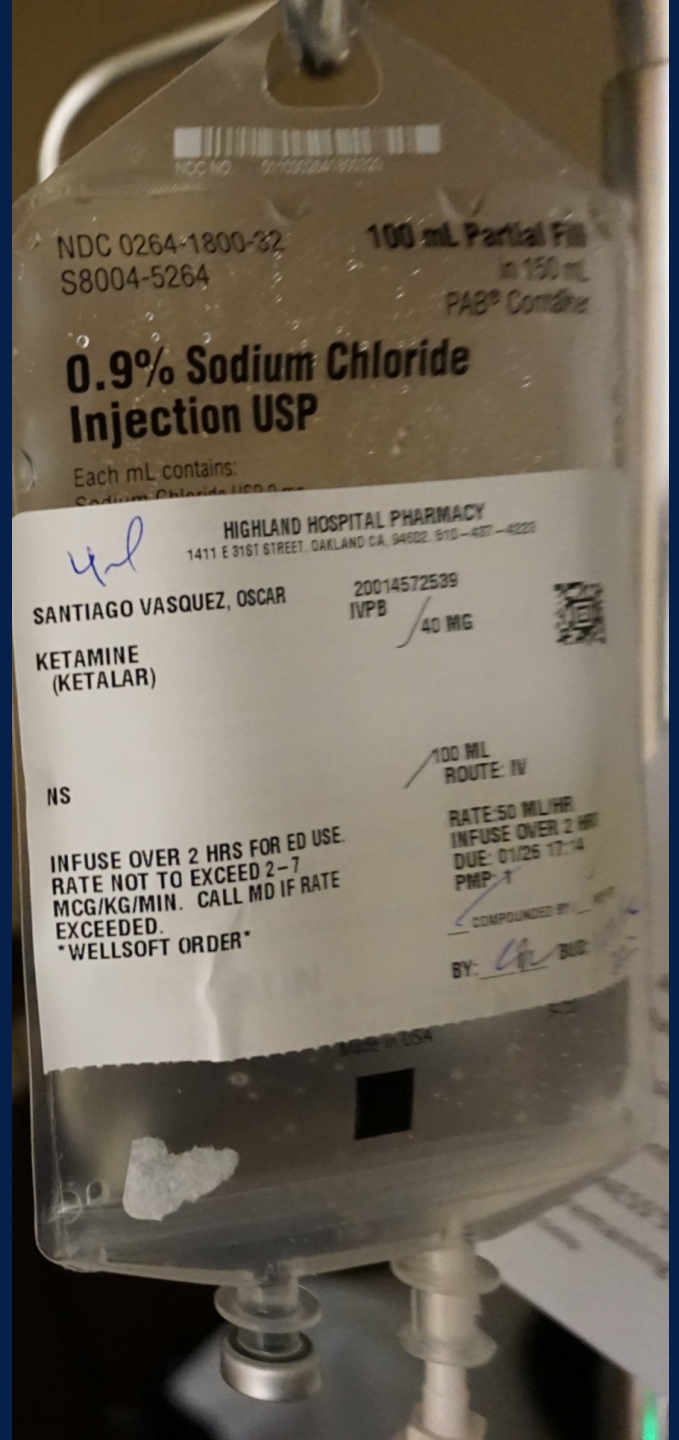


# How to use ketamine

- 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.

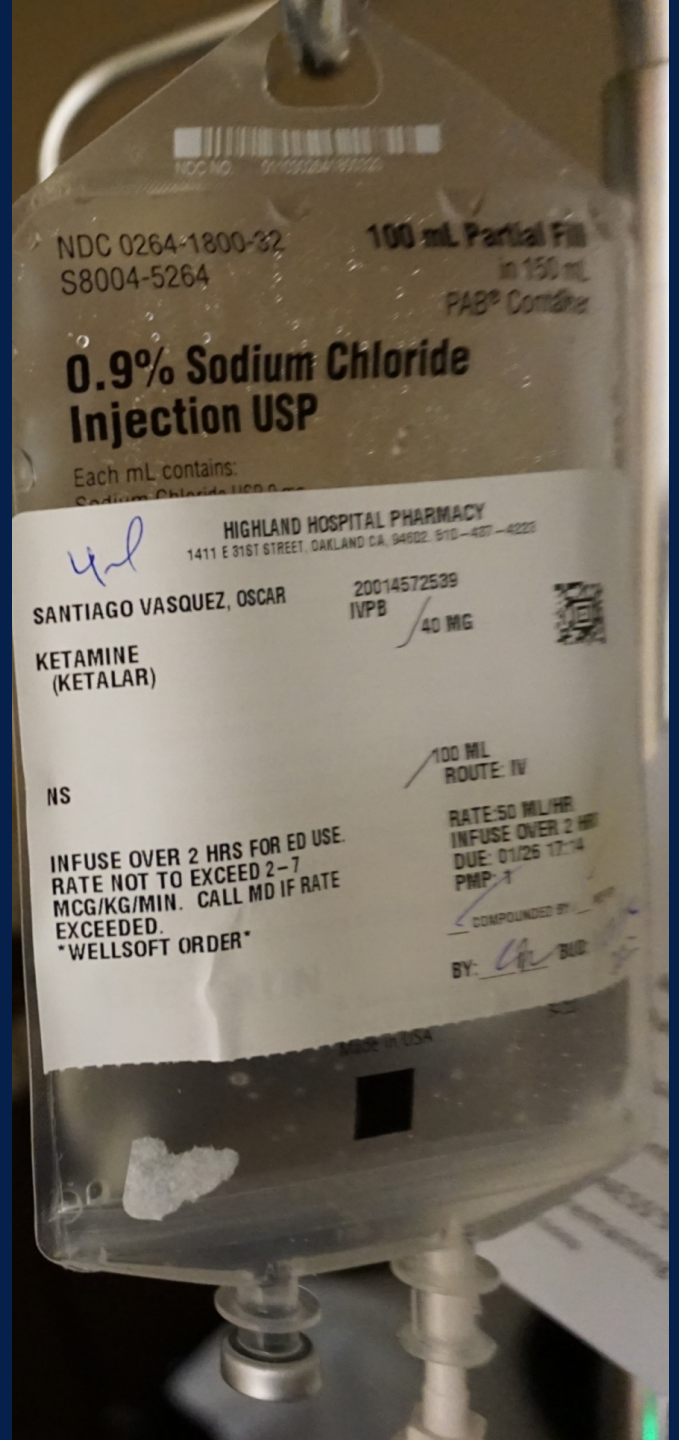
Motivational interviewing promotes placebo and enjoyment



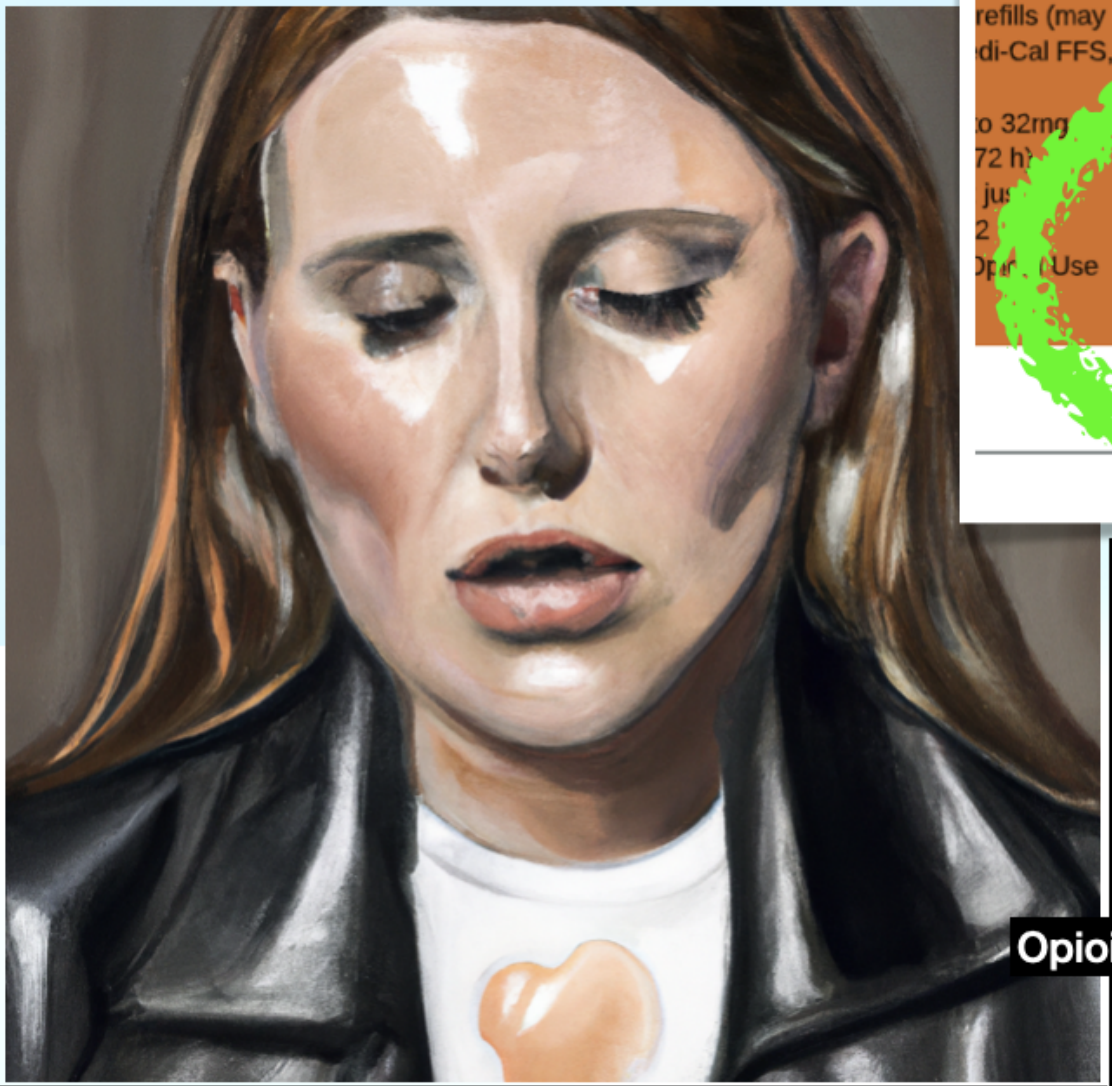
# When to Use Ketamine

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

- Symptom targeted
  - Pain
  - Precipitated withdrawal
  - Depression



# Case



HR 125, BP 170/90, 10/10 pain, vomiting, “feels terrible”

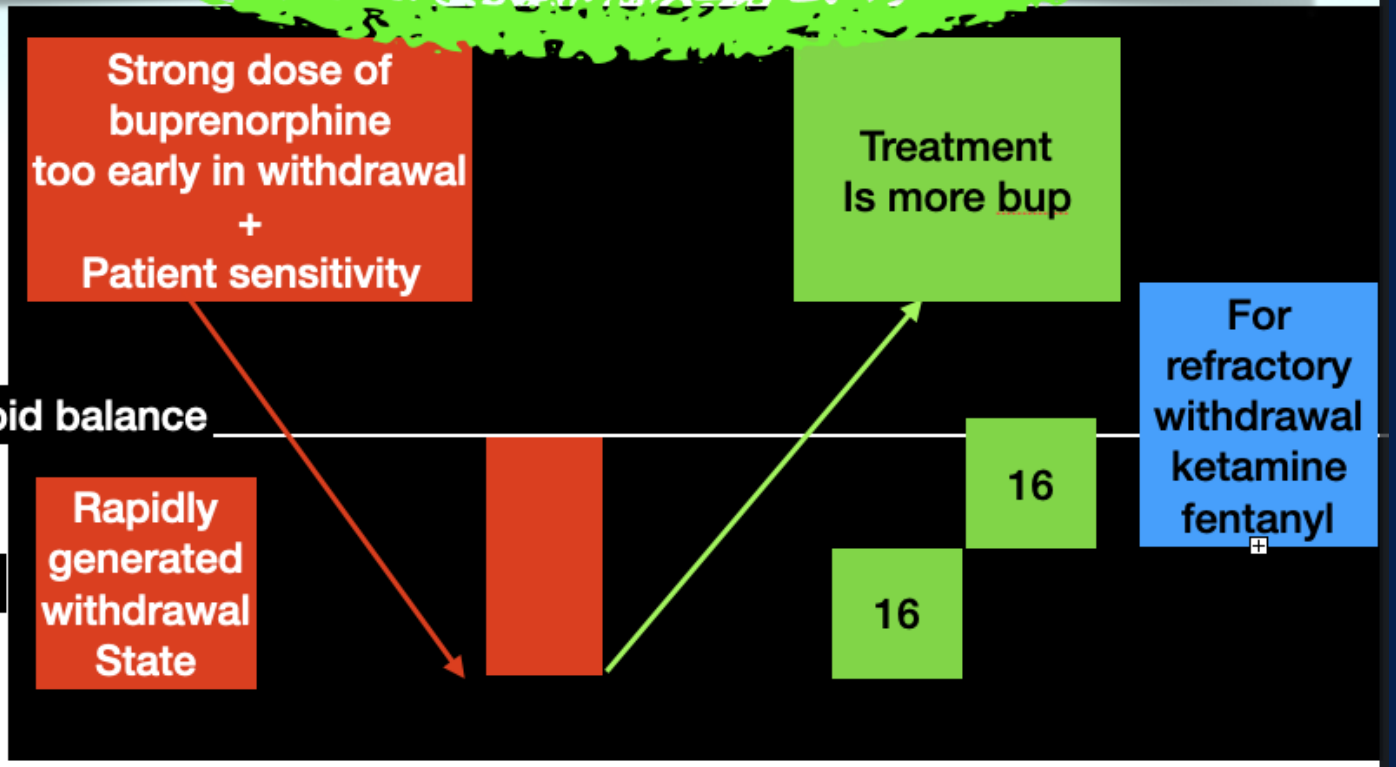
sufficient
e/naloxone
refills (may Rx
di-Cal FFS,
o 32mg
72 h
jus
2
Use

withdrawal after bup or full antagonist
(e.g. naloxone)--

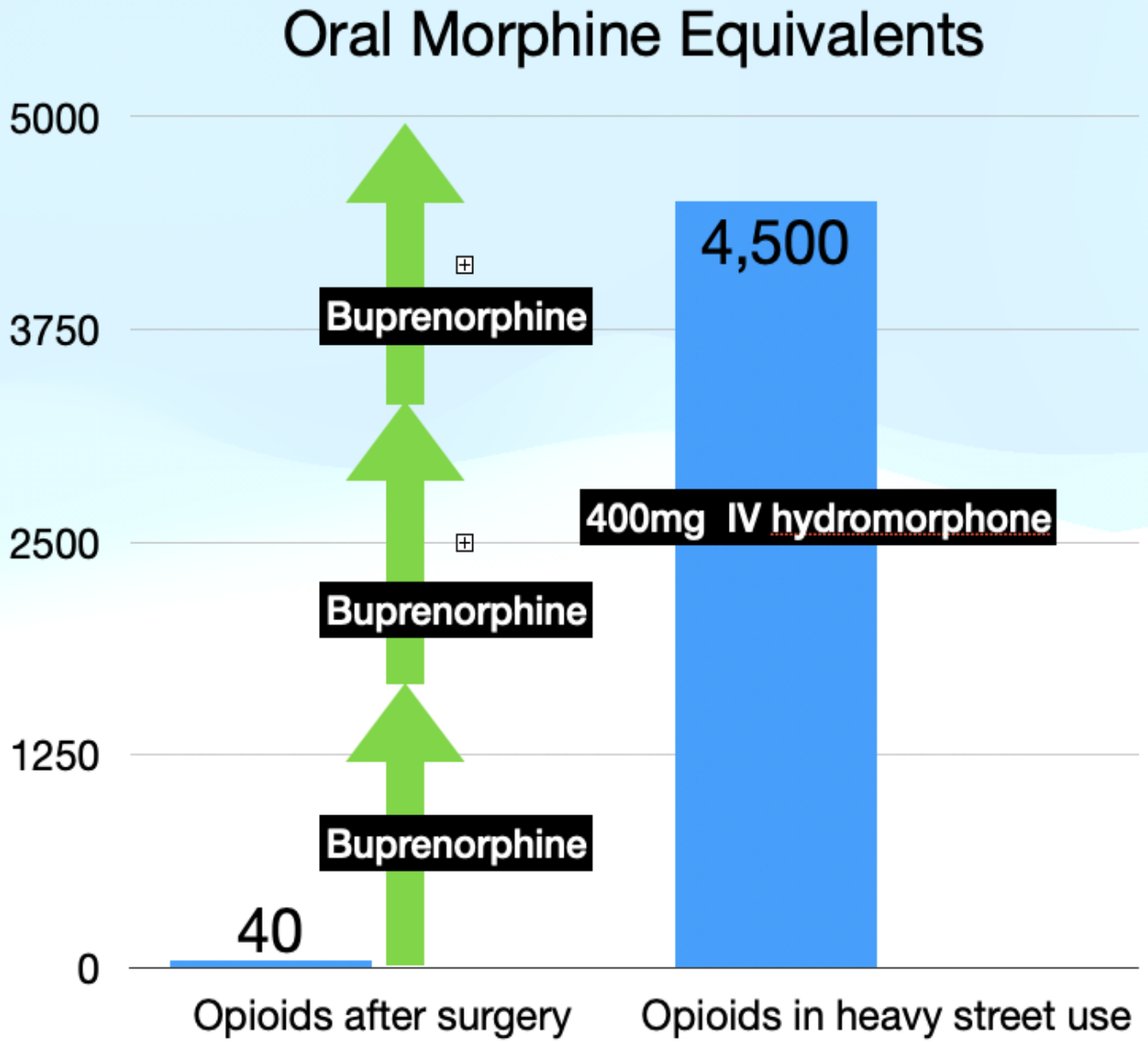
has has already completed
without opioids (typically >72
hrs from last use)
up: give Bup 8m
q6h prn cravings, usual dose
day. After first
day, consolidate dosing to daily.

**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 (ie 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
minutes or continuous infusion until calm)
drawal is managed, continue daily bup dose



# Case


Oral Morphine Equivalents
5000
3750
2500
1250
0
Buprenorphine
Buprenorphine
Buprenorphine
40
4,500
400mg IV hydromorphone
Opioids after surgery
Opioids in heavy street use

# 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

# Clinical Implementation - Prescribing

- 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

Radley DC, Finkelstein SN, Stafford RS. Off-label Prescribing Among Office-Based Physicians. Arch Intern Med. 2006;166(9):1021–1026. doi:10.1001/archinte.166.9.1021

# 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

Wittich, CM et al. Ten Common Questions (and Their Answers) About Off-label Drug Use. Mayo Clin Proc. October 2012;87(10):982-990 http://dx.doi.org/10.1016/j.mayocp.2012.04.017

*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)

FD&C Act Provisions that Apply to Human Drug Compounding, FDA. https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding

# 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

White and Brown Bagging Emerging Practices, Emerging Regulation. National Association of Boards of Pharmacy, 4/2018.

# 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

# Clinical Implementation – Encounter

- 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
- Silverstein et al.,“**Everything is not right anymore”: Buprenorphine experiences in an era of illicit fentanyl.** International Journal of Drug Policy 74 (2019) 76-83
- Rutgers ECHO,”Alternative Buprenorphine Induction Strategies,” Clement Chen, PharmD, 6/4/2021; https://sites.rutgers.edu/mat-coe/wp-content/uploads/sites/473/2021/06/06.04-ECHO_FINAL-1.pdf
- Randall et al., Enhancing Patient Choice: Using Self-administered Nasal Naloxone for Novel Rapid Buprenorphine Initiation. J Addict Med 2023;17(2):237-240.
- Hailozian et al., Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient with Fentanyl Use. J Addict Med 2022;16(4):483-487
- UpToDate.com “Ketamine: Drug Information.” ©2023
- Trujillo et al., Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991;251(4989):85-7.

# References, Dr. Grande


- Laskowski et al., A systematic review of intravenous ketamine for postoperative analgesia. Can J Anesth 2011; 58:911-923
- The Vaults of EROWID: https://erowid.org/chemicals/ketamine/ketamine.shtml
- Peltoniemi; Clin Pharmacokinet 2016; DOI 10.1007/s40262-016-0383-6
- Grande et al., Ultra-low Dose Ketamine and Memantine Treatment for Pain in an Opioid-Tolerant Oncology Patient. Anesth Analg 2008;107:1380 –3
- Grande-LA, Sublingual ketamine for rapid relief of suicidal ideation. Prim Care Companion CNS Disord 2017;19(0):16
- Grande (2018) Protocol for New Prescribers: Low-dose Sublingual Ketamine for Chronic Pain or Depression
- Grande et al., Poster at California Society of Addiction Medicine, 2022

# References, Dr. Herring


- Guo, J., Qiu, D., Gu, Hw. *et al.* Efficacy and safety of perioperative application of ketamine on postoperative depression: A meta-analysis of randomized controlled studies. *Mol Psychiatry* (2023). https://doi.org/10.1038/s41380-023-01945-z
- Herring et al., Emerging applications of low-dose ketamine for pain management in the ED. Am J Emerg Med 2013;31(2):416-419.
- Ahern et al., Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. Am J Emerg Med 2013;31:847-851.
- Ahern et al., The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med 2015 Feb;33(2):197-201.
- Ahern et al., Low-dose ketamine infusion for emergency department patients with severe pain. Pain Medicine 2015 Jul;16(7):1402-9.

# References, Dr. Herring


- Mizobuchi et al., Ketamine improves desensitization of mu-opioid receptors induced by repeated treatment with fentanyl but not with morphine. Biomolecules 2022 Mar 10;12(3):426.
- Sleigh et al., Trends in Anesthesia and Critical Care 2014;4:76-81
- Hashimoto K. Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. Biochem Pharm. 2020;177:113935-43.
- Hashimoto K. Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. Psychiatry Clin Neurosci. 2019;73:613–27.
- Hailozian et al., Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient with Fentanyl Use. J Addict Med 2022;16(4):483-487

# References, Dr. Hutch


- 21 U.S.C. 802(54)(A)–(G). Non-public health emergency-related exceptions to the Ryan Haight Online Pharmacy Consumer Protection Act of 2008.
- Bax Global Inc v Brenneman, Ohio 695 (Ohio Ct App 2007). https://casetext.com/case/bax-global-inc-v-indus-comm
- Canterbury v Spence, 464 F2d 772 (DC Cir 1972). https://casetext.com/case/canterbury-v-spence
- FD&C Act Provisions that Apply to Human Drug Compounding, FDA. https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding
- National Association of Boards of Pharmacy, 4/2018. White and Brown Bagging Emerging Practices, Emerging Regulation.
- Radley DC, Finkelstein SN, Stafford RS. Off-label Prescribing Among Office-Based Physicians. Arch Intern Med. 2006;166(9):1021–1026. doi:10.1001/archinte.166.9.1021
- Telemedicine Prescribing of Controlled Substances When the Practitioner and the Patient Have Not Had a Prior In-Person Medical Evaluation. 88 FR 12875. Federal Register, 3/1/2023. https://www.federalregister.gov/d/2023-04248
- Wittich, CM et al. Ten Common Questions (and Their Answers) About Off-label Drug Use. Mayo Clin Proc. October 2012;87(10):982-990 http://dx.doi.org/10.1016/j.mayocp.2012.04.017