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Psychiatry and Addictions Case Conference

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# IDENTIFYING AND MANAGING OPIOID WITHDRAWAL DURING BUPRENORPHINE INDUCTIONS


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# SPEAKER DISCLOSURES

No conflicts of interest

# PLANNER DISCLOSURES

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

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# OBJECTIVES

1. Understand the risk factors associated with buprenorphine-precipitated opioid withdrawal
2. Recognize evidence-based treatments of buprenorphine-precipitated opioid withdrawal
3. Discuss investigational treatments of buprenorphine-precipitated opioid withdrawal

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# WHY IS THIS IMPORTANT?

- Identify risk factors to help prevent precipitated withdrawal
- Help in counseling patients that are starting on buprenorphine for treatment of opioid use disorder (OUD)
- Manage symptoms of opioid withdrawal during buprenorphine induction effectively

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# OPIOID WITHDRAWAL SYNDROME

| | |
|---|---|
| **Resting Pulse Rate**: _____beats/minute<br>*Measured after patient is sitting or lying for one minute*<br>0 pulse rate 80 or below<br>1 pulse rate 81-100<br>2 pulse rate 101-120<br>4 pulse rate greater than 120 | **GI Upset**: *over last 1/2 hour*<br>0 no GI symptoms<br>1 stomach cramps<br>2 nausea or loose stool<br>3 vomiting or diarrhea<br>5 multiple episodes of diarrhea or vomiting |
| **Sweating:** *over past 1/2 hour not accounted for by room temperature or patient activity.*<br>0 no report of chills or flushing<br>1 subjective report of chills or flushing<br>2 flushed or observable moistness on face<br>3 beads of sweat on brow or face<br>4 sweat streaming off face | **Tremor** *observation of outstretched hands*<br>0 no tremor<br>1 tremor can be felt, but not observed<br>2 slight tremor observable<br>4 gross tremor or muscle twitching |
| **Restlessness** *Observation during assessment*<br>0 able to sit still<br>1 reports difficulty sitting still, but is able to do so<br>3 frequent shifting or extraneous movements of legs/arms<br>5 unable to sit still for more than a few seconds | **Yawning** *Observation during assessment*<br>0 no yawning<br>1 yawning once or twice during assessment<br>2 yawning three or more times during assessment<br>4 yawning several times/minute |
| **Pupil size**<br>0 pupils pinned or normal size for room light<br>1 pupils possibly larger than normal for room light<br>2 pupils moderately dilated<br>5 pupils so dilated that only the rim of the iris is visible | **Anxiety or Irritability**<br>0 none<br>1 patient reports increasing irritability or anxiousness<br>2 patient obviously irritable or anxious<br>4 patient so irritable or anxious that participation in the assessment is difficult |
| **Bone or Joint aches** *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*<br>0 not present<br>1 mild diffuse discomfort<br>2 patient reports severe diffuse aching of joints/muscles<br>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort | **Gooseflesh skin**<br>0 skin is smooth<br>3 piloerrection of skin can be felt or hairs standing up on arms<br>5 prominent piloerrection |
| **Runny nose or tearing** *Not accounted for by cold symptoms or allergies*<br>0 not present<br>1 nasal stuffiness or unusually moist eyes<br>2 nose running or tearing<br>4 nose constantly running or tears streaming down cheeks | Total Score _____<br>The total score is the sum of all 11 items<br>Initials of person completing assessment: _____ |

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# WHAT IS PRECIPITATED WITHDRAWAL

- Buprenorphine is a high-affinity, partial-agonist opioid
  - When administered in patient with tolerance to opioids, will buprenorphine will displace full-agonist opioids, causing a decrease in the signaling of the opioid receptor
  - Usually defined as an increase in COWS score (greater than 5-6) 30-60 minutes after receiving buprenorphine
- Challenges in the era of fentanyl
  - Fentanyl is highly potent, has high affinity for opioid receptor, and is highly lipophilic
  - Chronic fentanyl use may increase receptor desensitization and internalization
  - Variable experiences from person to person, and varied experiences of opioid withdrawal symptoms

Greenwald, Mark K., et al. "A neuropharmacological model to explain buprenorphine induction challenges." *Annals of Emergency Medicine* 80.6 (2022): 509-524.
Weimer, Melissa B., et al. "ASAM clinical considerations: buprenorphine treatment of opioid use disorder for individuals using high-potency synthetic opioids." *Journal of addiction medicine* 17.6 (2023): 632-639.

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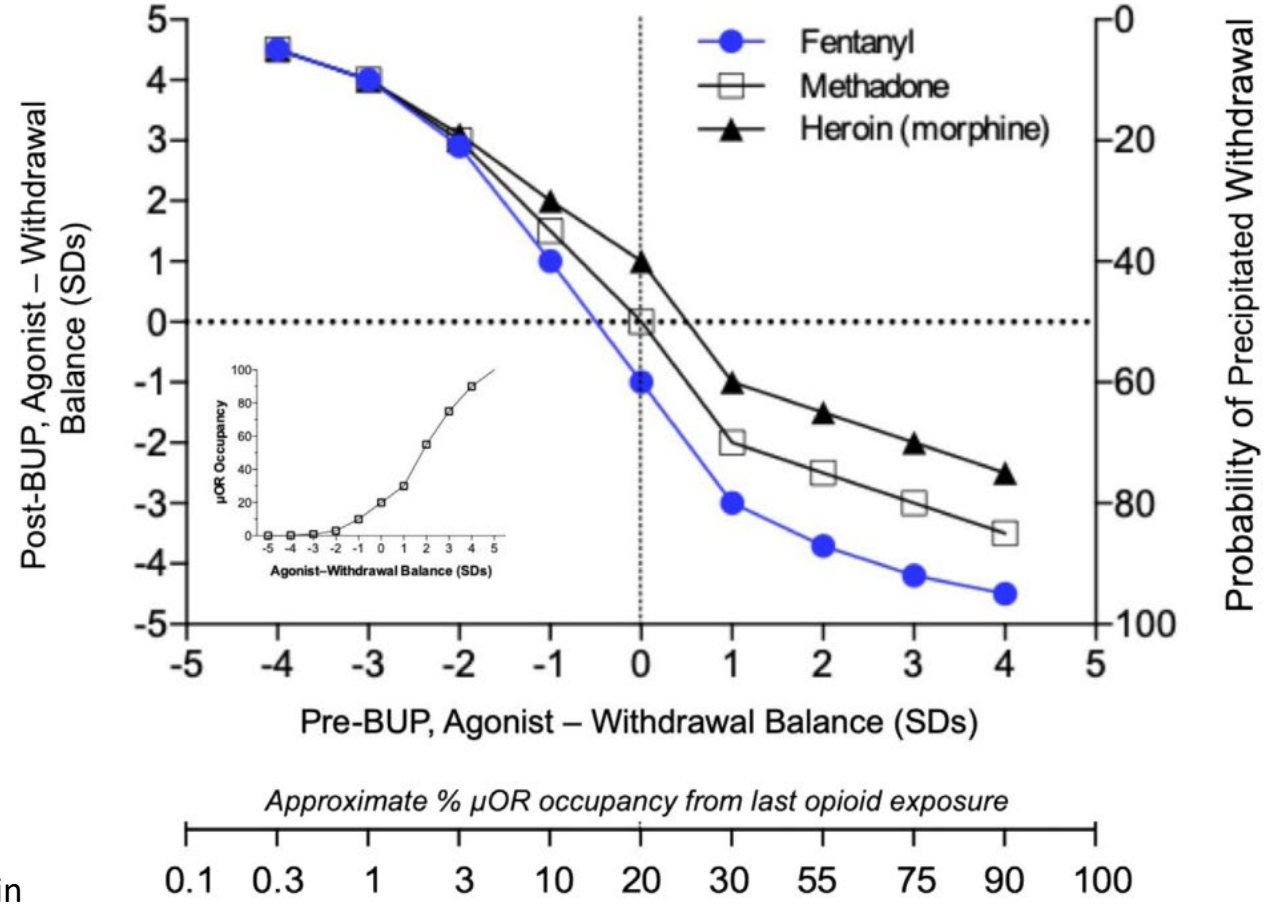
# WHAT IS PRECIPITATED WITHDRAWAL




Greenwald, Mark K., et al. "A neuropharmacological model to explain buprenorphine induction challenges." *Annals of Emergency Medicine* 80.6 (2022): 509-524.

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# HOW PREVALENT IS PRECIPITATED WITHDRAWAL?

- Data is variable and still evolving in the era of fentanyl

- Is patient experiencing precipitated withdrawal, or withdrawal from fentanyl?

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# PREVALENCE OF PRECIPITATED WITHDRAWAL

- In one study looking at self-reported patient survey data for 1163 patients entering treatment...
  - People that had used fentanyl within 24 hours of starting buprenorphine 5 times higher odds (OR 5.2) of reporting severe opioid withdrawal symptoms compared to OR 3.4 for patients with fentanyl use within 48 hours of starting buprenorphine, and no increased odds when last use was 72 hours prior
  - 41.5% of patients reported they knew someone that had been using fentanyl and experienced precipitated withdrawal

Varshneya, Neil B., et al. "Evidence of buprenorphine-precipitated withdrawal in persons who use fentanyl." *Journal of addiction medicine* (2022)


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# PREVALENCE OF PRECIPITATED WITHDRAWAL

- Much of the data on high-dose initiation is from studies in the ED
- Large multisite clinical trial from 2020 – 2022, 1200 patients were initiated on buprenorphine in the ED
  - 69.5% confirmed fentanyl on UDS, 0.76% (9 cases) of precipitated withdrawal
- Retrospective review of ED buprenorphine initiations in 2020, with fentanyl use defined by patient report (87 of 896 patients using opioids)
  - Precipitated withdrawal documented in 1.6% of patients
- Retrospective study of a hospital and ED-based sample of 226 patients in 2020-2021, and included patients given a “traditional” vs a high-dose buprenorphine initiation
  - Precipitated withdrawal documented in 11.5 % of patients
  - Of note, 40% of patients in original sample excluded do to no documented COWS after initiation
  - PW associated with higher urine fentanyl concentrations

D’Onofrio, Gail, et al. "Incidence of precipitated withdrawal during a multisite emergency department–initiated buprenorphine clinical trial in the era of fentanyl." *JAMA Network Open* 6.3 (2023)
Snyder, Hannah, et al. "High-dose buprenorphine initiation in the emergency department among patients using fentanyl and other opioids." *JAMA network open* 6.3 (2023)
Thakrar, Ashish P., et al. "Buprenorphine-precipitated withdrawal among hospitalized patients using fentanyl." *JAMA Network Open* 7.9 (2024)

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# TREATMENT AND PREVENTION OF PRECIPITATED WITHDRAWAL

- Brief overview of types of inductions
  - Low-dose crossover vs high dose initiation
- More buprenorphine!
- Adjunct medications for opioid withdrawal
- Investigational treatments

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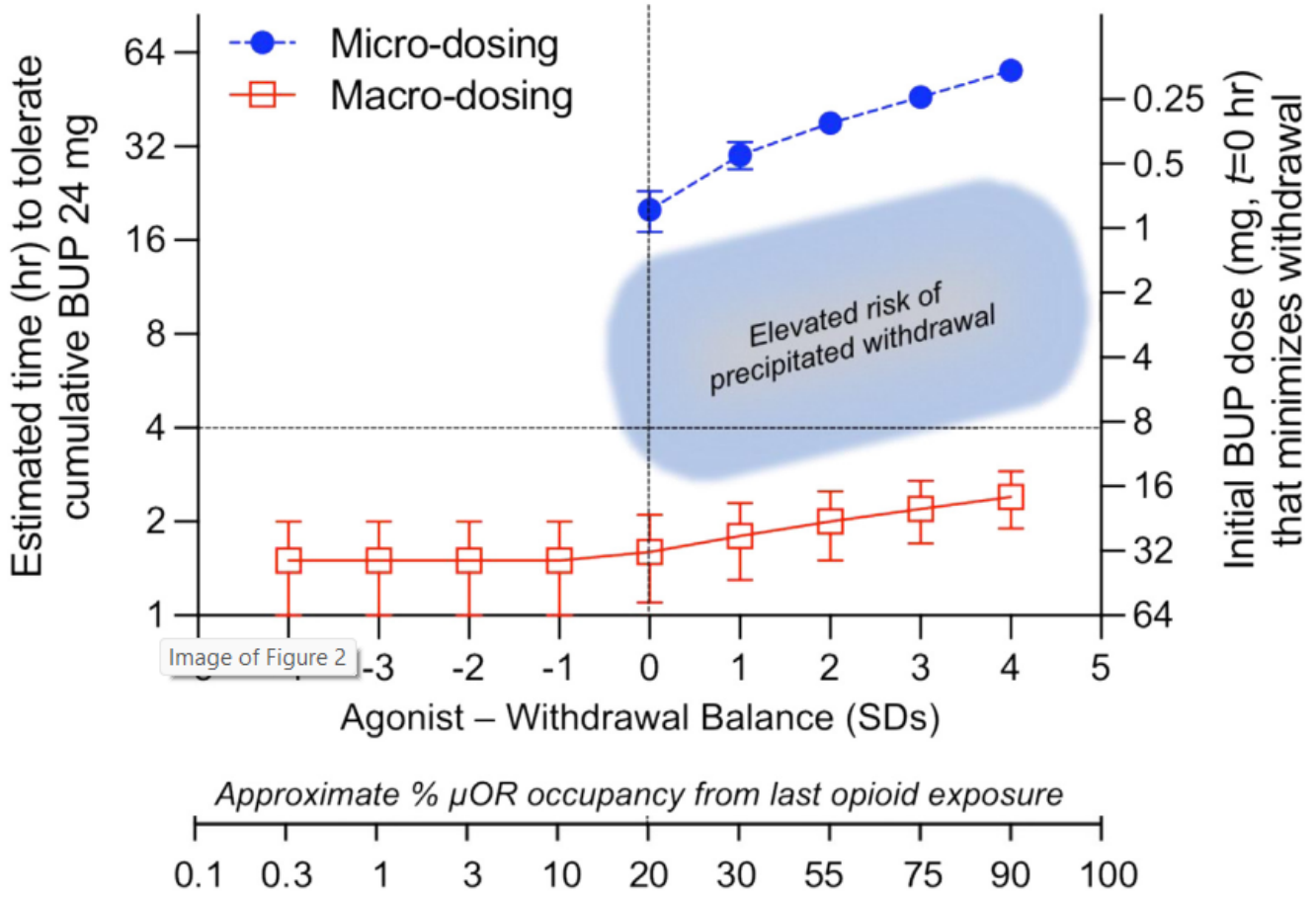


Image of Figure 2

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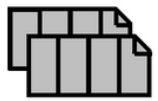
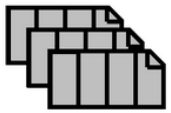
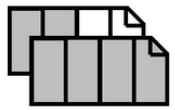
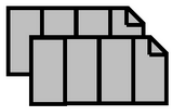
# LOW DOSE CROSS-OVER PROTOCOL

| | DAY 1 ___/___/___ | DAY 2 ___/___/___ | DAY 3 ___/___/___ | DAY 4 ___/___/___ | DAY 5 ___/___/___ |
|---|---|---|---|---|---|
| How much do I take of a 2 mg strip? | 1/4 strip daily  | 1/2 strip daily  | 1 strip daily  | 2 strips daily  | 3 strips daily  |

| | DAY 6 ___/___/___ | DAY 7 ___/___/___ | DAY 8 ___/___/___ |
|---|---|---|---|
| How much do I take of an 8 mg strip? | 1 strip daily  | 1 & 1/2 strips daily  | 2 strips daily  |

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# HIGH DOSE INITIATION

## Starting buprenorphine at home

**DAY 1**

**Wait at least 12-24 hours since last heroin or fentanyl use.**

*Take other prescribed medications to treat symptoms*

**Moderate withdrawal** →

*Means 3+ of the following:*
*Restlessness // Yawning*
*Runny nose // Big pupils*
*Watery eyes // No appetite*
*Stomach cramps // Body aches*
*Shaking/twitching // Sweats*
*Chills // Goosebumps*
*Nausea or vomiting // Diarrhea*

**Take 2 tablets or films all at once**

**16 mg**

**Wait 30-60 minutes** →

**Take 1-2 additional tablets or films if needed**

**8 mg** **8 mg**

*Do not take more than 4 tablets or films (32 mg) the first day*

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# PREVENTING PRECIPITATED WITHDRAWAL

- Timing of buprenorphine initiation is key!
  - patient history
  - evaluation of objective withdrawal signs

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# TREATMENT OF BUPRENORPHINE ASSOCIATED PRECIPITATED WITHDRAWAL

- More buprenorphine!
  - Patients may safely receive 24 to 32 mg of buprenorphine within the first day of initiation. Often found to be helpful for treatment of symptoms of opioid withdrawal
  - At 32mg, 96-98% of opioid receptor is occupied by buprenorphine

- Is it safe?
  - Ceiling effect on the dangerous side-effects of opioids, namely respiratory depression
  - Studies have demonstrated safety of single doses of 32mg, and up to as high as 96mg (in one study, only 2 patients at 96mg had adverse effects of hypotension treated with oral hydration)

Efficacy: Weimer, Melissa B., et al. "ASAM clinical considerations: buprenorphine treatment of opioid use disorder for individuals using high-potency synthetic opioids." *Journal of addiction medicine* 17.6 (2023): 632-639.
Occupancy: Grande, Lucinda A., et al. "Evidence on buprenorphine dose limits: a review." *Journal of addiction medicine* 17.5 (2023): 509-516.
Safety: Analgesic Effects of Hydromorphone versus Buprenorphine in Buprenorphine-Maintained Individuals
Ahmadi, Jamshid, et al. "Single high-dose buprenorphine for opioid craving during withdrawal." *Trials* 19 (2018): 1-7.

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# ANCILLARY MEDICATIONS

- All patients that are experiencing opioid withdrawal should receive treatment of specific symptoms

- Consider pre-treatment based on patient prior experience

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# ANCILLARY MEDICATIONS

**Table 4. Ancillary Medications to Treat Complicated Opioid Withdrawal[1-4]**

| **Medications** (Alphabetical Order) | **Class/action** | **Target** |
|---|---|---|
| Baclofen 20 mg oral three times a day as needed | Gaba-B agonist | Anxiety, tremor |
| Benzodiazepines<br>Ex. Lorazepam 0.5-1mg TID PRN | Sedative Hypnotic | Anxiety |
| Clonidine 0.1-0.3 mg oral four times a day as needed[5] | Alpha-2 agonist | Anxiety, restlessness |
| Dicyclomine 10mg oral four times daily as needed | Anti-cholinergic, relaxes smooth muscles of the intestines | Abdominal cramping |
| Gabapentin 300-900 mg oral three times a day | Reduces central nervous system excitation | Anxiety |
| Hydroxyzine 25-50 mg oral every 4-6 hours as needed | Antihistamine | Anxiety |
| Ibuprofen 400 mg oral every 6 hours | Non-steroidal medication | Pain |
| Lofexidine 0.54mg oral four times a day as needed[5] | Alpha-2-agonist | Anxiety, restlessness |
| Loperamide 4 mg oral every 2-4 hours as needed | Opioid receptor agonist that acts on the mu opioid receptors in the mesenteric plexus of the large intestine | Diarrhea |
| Ondansetron 4 mg oral every 4 hours | HT3 receptor antagonist | Nausea |
| Pramipexole 0.25 mg oral three times a day as needed | Dopamine D3 agonist | Restlessness |
| Short acting full opioid agonists (e.g., oxycodone, hydromorphone)[6] * | Opioid | Pain, withdrawal |
| Trazodone 50-100 mg oral at night as needed | 5-HT2 and alpha-1 antagonist | Insomnia |

*Given in the inpatient setting only unless indicated for pain

Weimer, Melissa B., et al. "ASAM clinical considerations: buprenorphine treatment of opioid use disorder for individuals using high-potency synthetic opioids." *Journal of addiction medicine* 17.6 (2023): 632-639.

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# ANCILLARY MEDICATIONS – FULL AGONIST OPIOIDS

- If patient is having refractory opioid withdrawal symptoms despite treatment with buprenorphine and ancillary medications, consider full-agonist opioid therapy
  - Patient in a monitored setting
  - Will require higher than usual doses due to partial-agonist blockade from buprenorphine
  - Higher affinity opioids most likely to be helpful

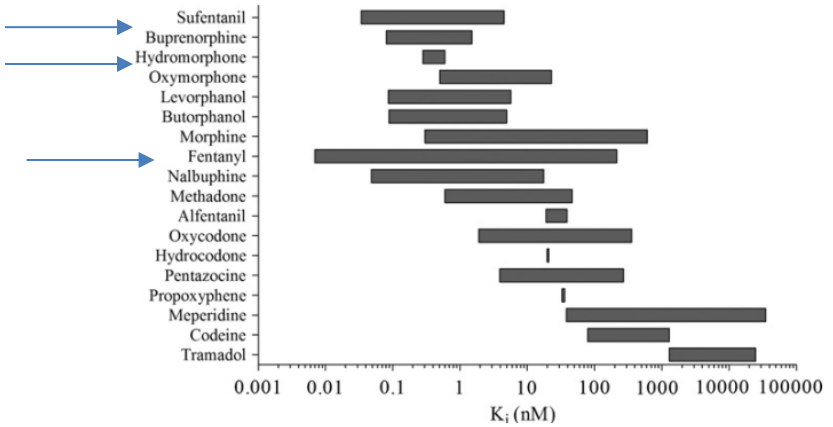


**Fig. 4.** Range of literature $K_i$ values for opioid drugs in MOR inhibition assays. (Alt et al., 1998; Bot et al., 1998; Brasel et al., 2008; Carroll et al., 1988; Chang et al., 1980; Chen et al., 1991; Chen et al., 1993; Childers et al., 1979; de Jong et al., 2005; Emmerson et al., 1996; Leysen et al., 1983; Nielsen et al., 2007; Raffa et al., 1992; Raffa et al., 1993; Raynor et al., 1994; Toll et al., 1998; Traynor and Nahorski, 1995; Tzschentke et al., 2007; Wentland et al., 2009; Yeadon and Kitchen, 1988).

Volpe, Donna A., et al. "Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs." *Regulatory Toxicology and Pharmacology* 59.3 (2011): 385-390

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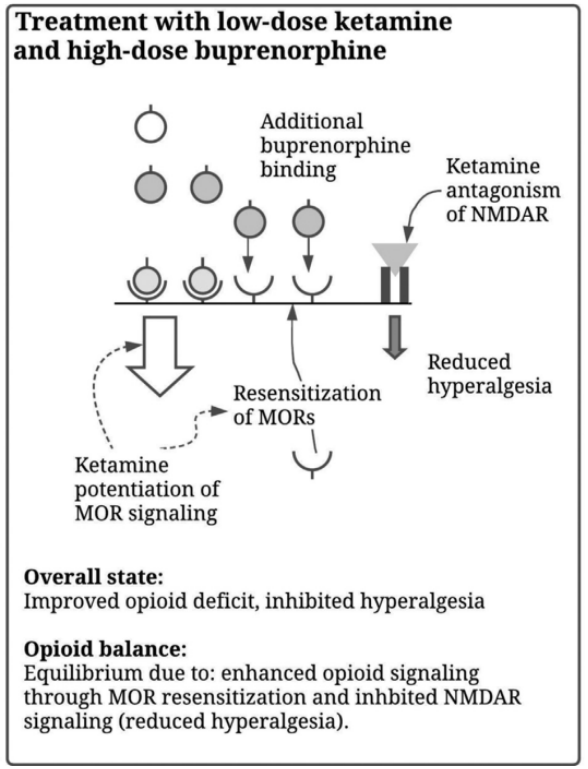
# INVESTIGATIONAL THERAPIES: KETAMINE

- Theoretical benefit via 1) Reduction in hyperalgesia and central sensitization via NMDA agonism 2) potentiation of opioid receptor activity 3) resensitization of mu opioid receptor in chronic users 4) reduced depressive symptoms, decreased stress response
- Doses vary in case reports and protocols:
  - 0.3-0.6mg/kg loading dose, can be followed by

  a low dose continuous infusion if needed (0.1-0.3mg/kg/hr)




Hailozian, Christian, et al. "Synergistic effect of ketamine and buprenorphine observed in the treatment of buprenorphine precipitated opioid withdrawal in a patient with fentanyl use." *Journal of addiction medicine* (2022).

Christian, Nicholaus J., et al. "Precipitated opioid withdrawal treated with ketamine in a hospitalized patient: a case report." *Journal of Addiction Medicine* 17.4 (2023): 488-490.

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# SUMMARY

- Be thoughtful with approach to induction strategy – patient history is key
- Answer is almost always…more bupe! Its safe and effective
- Everyone should have ancillary medications available during initiation of buprenorphine
- Consider higher level of care for additional supportive therapies if needed


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# QUESTIONS?

https://www.usgs.gov/geology-and-ecology-of-national-parks/mount-rainier-ecology

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- Greenwald, Mark K., et al. "A neuropharmacological model to explain buprenorphine induction challenges." *Annals of Emergency Medicine* 80.6 (2022): 509-524.
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