Initiating Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid Withdrawal in the Emergency Department

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National Drug Abuse Treatment Clinical Trials Network

Disclosure Information

NIH HEAL Initiative: Results from Selected NIDA's Clinical Trials Network Studies

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April 25, 2025

- No Conflicts of Interest to Disclose
- 7 day-injectable buprenorphine was donated to NIDA in the context of a NIDA research study

Research Funding

- NIDA 3UG1DA015831-19S1; CTN 0099 (PIs: D'Onofrio/Fiellin)

- NIAAA 1R01AA030568-01 (PI: Hawk)
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- NIDA 1R61DA059169-01 (PIs: Hawk/Venkatesh/Taylor)
- Foundation for Opioid Response (PI: Hawk)
- Elevance Foundation (PI: Venkatesh)

Learning Objectives

At the end of this presentation, participants should be able:

- To identify rationale and strategies used to initiate buprenorphine in the Emergency Department setting.
- To describe how the use of injectable buprenorphine formulation differs from sublingual.
- To discuss the use of a 7-day injectable extended-release buprenorphine in ED settings among patients with OUD who present with minimal to mild withdrawal symptoms.
- To discuss the rationale behind ED INNOVATION, a recently completed clinical trial comparing the use of a 7-day injectable buprenorphine formulation to sublingual for treatment initiation in the ED.

We Know…

Treatment for OUD Works

Why focus on the ED?

Because that's where the patients are!

14% of drug related ED visits (1.3 million) involved opioids in 2021

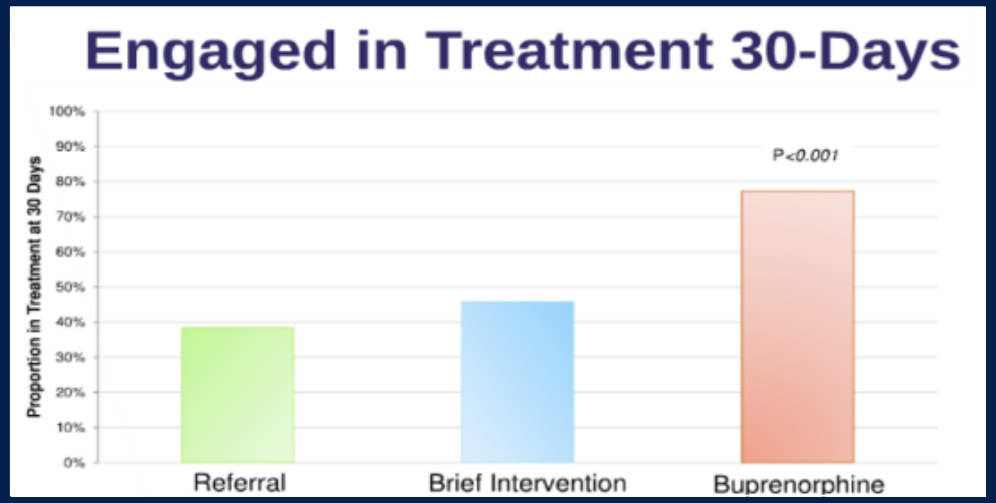
Preliminary Findings from Drug-Related Emergency Department Visits, 2021; SAMHSA/DAWN 2022

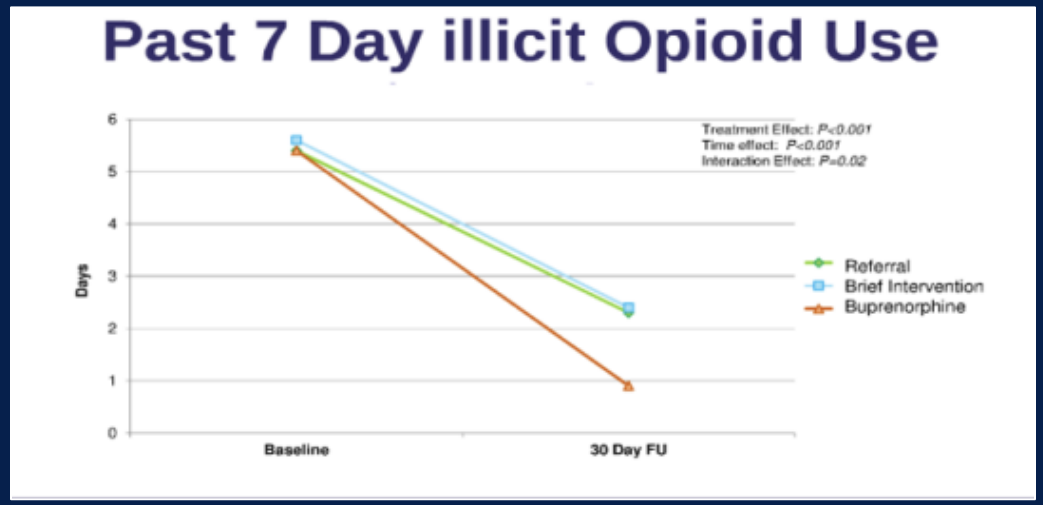
Research

Original Investigation

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD





- COWS ≥ 12 → 8 mg SL buprenorphine
- One half of those randomized to BUP arm received unobserved/home initiation

D'Onofrio JAMA 2015

American College of Emergency Physicians®

Extra Motivation

THE PRACTICE OF EMERGENCY MEDICINE/CONCEPTS

Consensus Recommendations on the Treatment of Opioid Use Disorder in the Emergency Department

Kathryn Hawk, MD, MHS*; Jason Hoppe, DO; Eric Ketcham, MD; Alexis LaPietra, DO; Aimee Moulin, MD; Lewis Nelson, MD; Evan Schwarz, MD; Sam Shahid, MBBS, MPH; Donald Stader, MD; Michael P. Wilson, MD; Gail D'Onofrio, MD, MS

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The treatment of opioid use disorder with buprenorphine and methadone reduces morbidity and mortality in patients with opioid use disorder. The initiation of buprenorphine in the emergency department (ED) has been associated with increased rates of outpatient treatment linkage and decreased drug use when compared to patients randomized to receive standard ED referral. As such, the ED has been increasingly recognized as a venue for the identification and initiation of treatment for opioid use disorder, but no formal American College of Emergency Physicians (ACEP) recommendations on the topic have previously been published. The ACEP convened a group of emergency physicians with expertise in clinical research, addiction, toxicology, and administration to review literature and develop consensus recommendations on the treatment of opioid use disorder in the ED. Based on literature review, clinical experience, and expert consensus, the group recommends that emergency physicians offer to initiate opioid use disorder treatment with buprenorphine in appropriate patients and provide direct linkage to ongoing treatment for patients with untreated opioid use disorder. These consensus recommendations include strategies for opioid use disorder treatment initiation and ED program implementation. They were approved by the ACEP board of directors in January 2021. [Ann Emerg Med. 2021;■:1-9.]

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2021.04.023

AMERICAN SOCIETY OF ADDICTION MEDICINE FOUNDED 1954 ASAM

Strategies for ED Buprenorphine Initiation

- Standard ED Dosing
- High Dose
- Injectable Formulations

Rationale for High Dose

Rapid titration to therapeutic buprenorphine levels
- Minimizing craving and incompletely treated withdrawal

Lasts up to 72 hours
- Providing a safety net if unable to access Rx next day
- May be less true in context of high dose fentanyl use

Compelling retrospective safety data

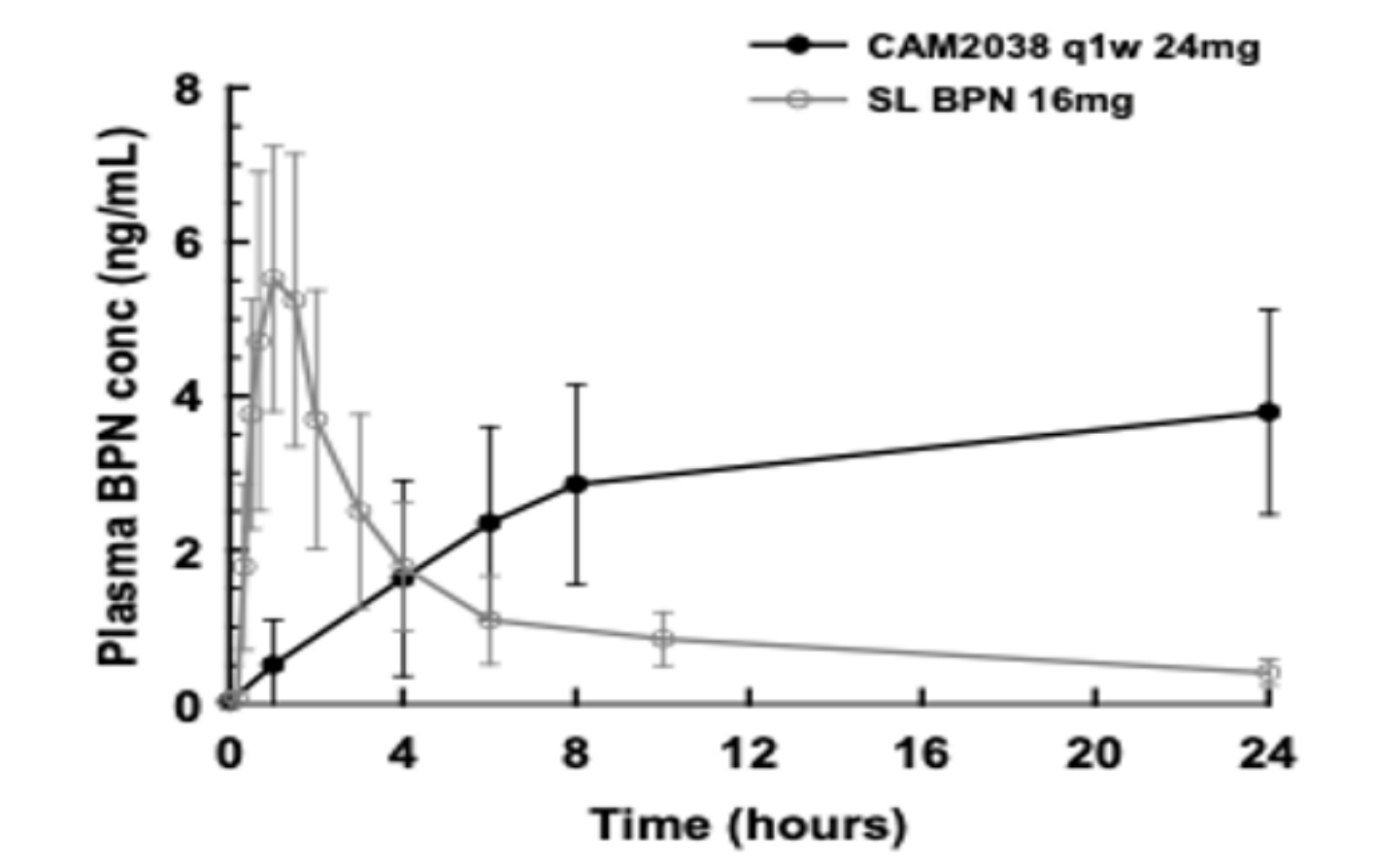
Herring et al, JAMA Netw Open 2021, Snyder et al, JAMA Netw Open 2023

Injectable Formulations

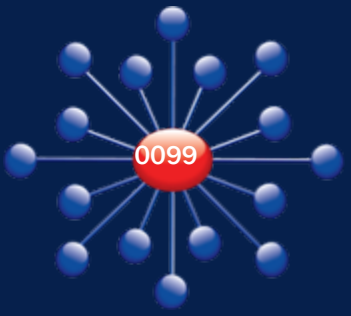
	Monthly buprenorphine injection	Weekly and monthly injection (CAM-2038)
Approval	Australia & USA	Australia, EMA, USA
Indications	Adults with moderate-severe OUD, tolerating SL bup at 8-24 mg/day for at least 7 days.*	Treatment OUD (age 16yrs +) within framework of medical, psychological and social treatment; SL lead in dose
Mean bup concentration at steady state (ng/mL)	100 mg injection: 3.21 300 mg injection: 6.54	Variable depending on dose but >1

Modified from Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med Volume 13, Number 2, March/April 2019

Pharmacokinetics of 7-day XR- & SL- Buprenorphine



ED INNOVATION Ancillary Study Objective



To estimate changes in opioid withdrawal signs and symptoms among patients with minimal signs of withdrawal defined as COWS score < 8; and assess feasibility and safety of induction with XR-BUP

D'Onofrio et al. Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid Withdrawal, JAMA Netw Open, 2024

Team

Yale University School of Medicine

Yale NewHaven Health
Yale New Haven Hospital

HIGHLANDHOSPITAL
A member of Alameda Health System

ALAMEDA HEALTH SYSTEM
San Leandro Hospital

Penn Medicine
Penn Presbyterian Medical Center

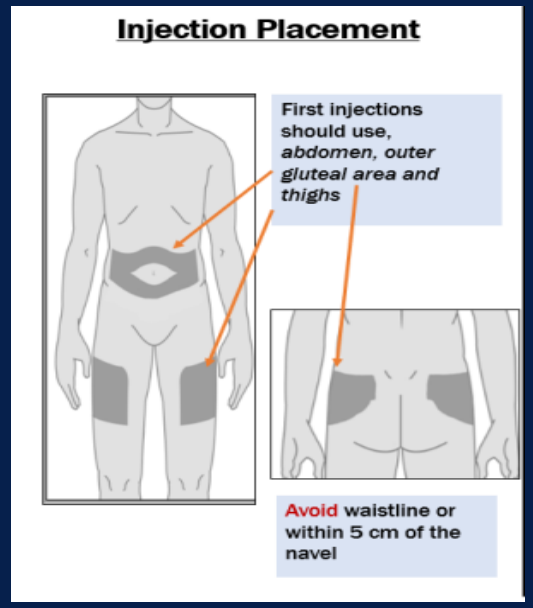
University of Kentucky

Expert Consultants

Rhode Island Hospital
Lifespan. Delivering health with care.

Intervention

- Injection of 24mg of CAM2038 (equivalent to 16 mg of buprenorphine daily)
- 4-hour intense ED observation period to assess clinical course and signs of precipitated withdrawal
- Referral for ongoing OUD care within 7 days



Precipitated Withdrawal

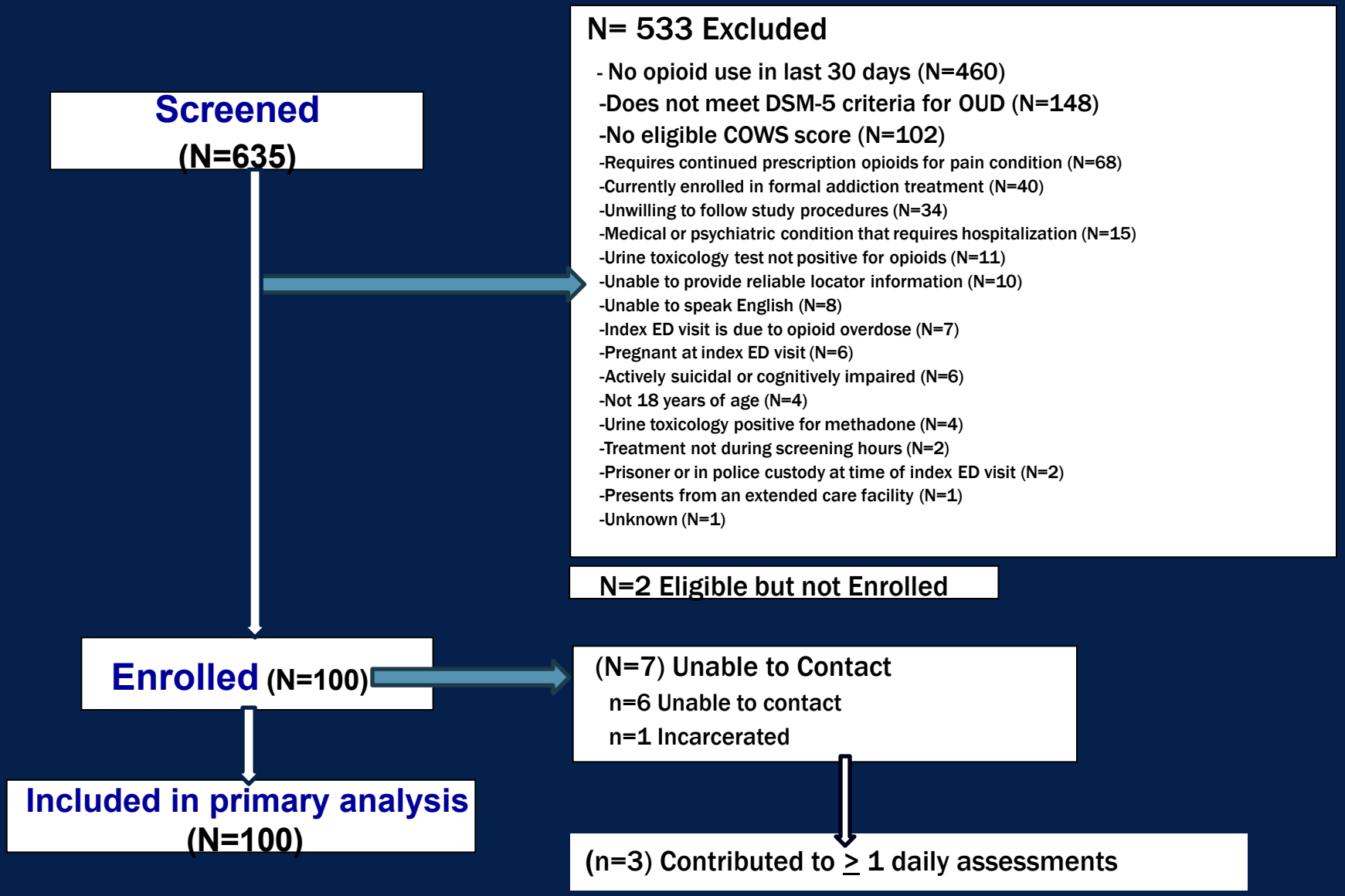
- Rapid onset of withdrawal symptoms within 1-hour of administration of buprenorphine (described for SL-BUP)

- Assessment is based on rapidity of onset of withdrawal symptoms and clinical factors, similar to when a patient receives full naloxone rescue. COWS scores reflect this rapid deterioration and skyrocket to moderate/severe levels.

- All potential PW cases adjudicated by independent experts Michelle Lofwall and Sharon Walsh.

Rosado, Alcohol Depend 2007;90(2-3):261-269 https://doi.org/10.1016/j.drugalcdep.2007.04.006
Comer S, et al. National practice guideline for the use of medications in the treatment of addiction involving opioid use. American Society for Addiction Medicine. 2015;66.

CONSORT Diagram

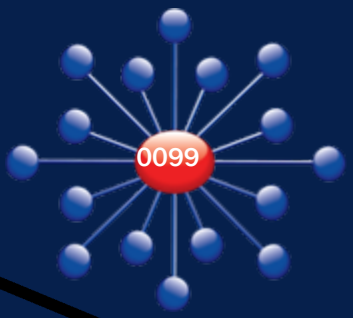


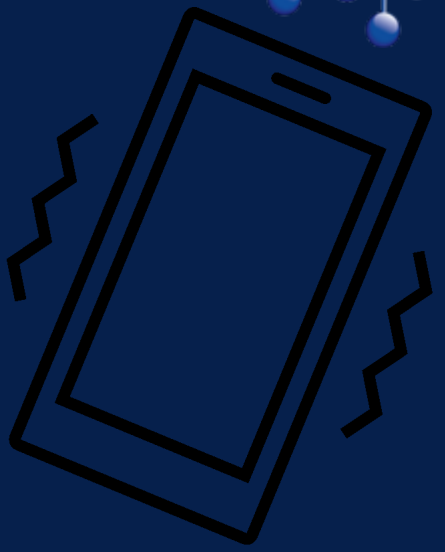
Monitoring and Observation Pre & Post Injection

Assessments	Pre-Injection	Post-Injection Time Points								
		Immediately after Injection	30 mins	60 mins	90 mins	120 mins	150 mins	180 mins	210 mins	240 mins
Vital Signs	X		X	X	X	X	X	X	X	X
COWS	X		X	X	X	X	X	X	X	X
Objective Opioid Withdrawal Scale (OOWS)	X		X	X	X	X	X	X	X	X
Adjective Rating Scale for Withdrawal (ARSW)	X									X
Pupillary Diameter	X		X	X	X	X	X	X	X	X
Desire to Use	X									X
Bad Drug Effects	X		X							X
Post-Injection Medications			X	X	X	X	X	X	X	X
Pain Assessment Numerical Rating Scale		X	X							X
Local Tolerability Scale			X							X
Precipitated Withdrawal		Triggered based on clinical observation and COWS scores								

Patient self-report days 1-7

Qualtrics survey via telephone





Daily Follow-Up Survey

Dear Project ED-INNOVATION participant, thank you for completing the following questions!

1. Have you used any opioids not prescribed for you during the past 24 hours?

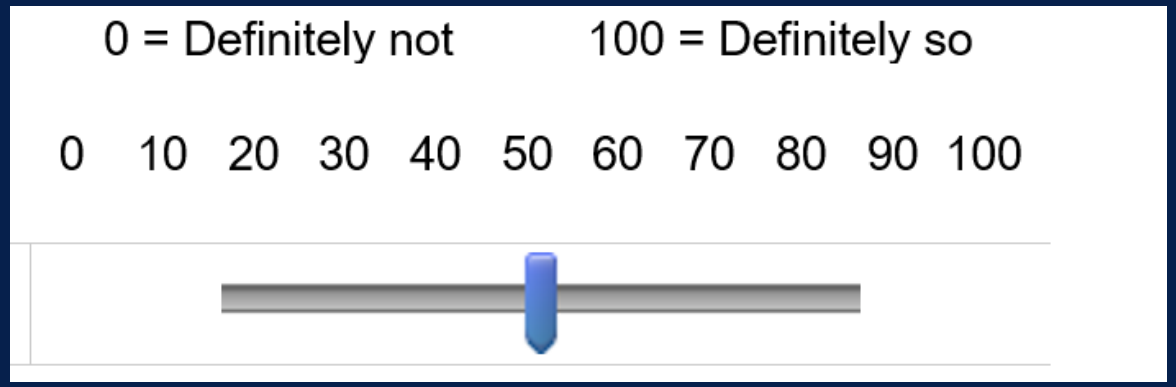
   If “yes” what did you use? (Drop down menu)

2. Have you used any other drugs not prescribed for you during the past 24 hours?

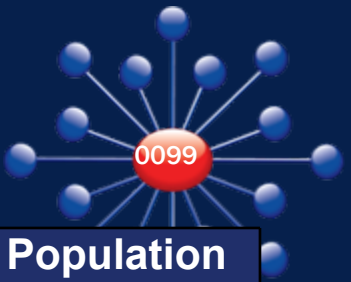
   If “yes” what did you use? (Drop down menu)

3. Use the slider to indicate how much you desire opioids at the moment

At this moment, I desire opioids: ()



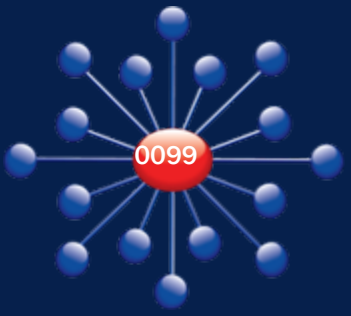
Results: Baseline Characteristics



	COWS 4-7 n=63	COWS 0-3 n=37	Full Population COWS 0-7 N=100
Sex: Male	47 (74.6%)	25 (67.7%)	72 (72.0%)
Age (Mean (SD))	37 (9.21)	36 (7.87)	37 (8.70)
Ethnicity Hispanic or Latino	9 (14.3%)	4 (10.8%)	13 (13.0%)
Race			
Black or African American	19 (30.2%)	16 (43.2%)	35 (35.0%)
White	34 (54.0%)	17 (45.9%)	51 (51.0%)
Other	8 (12.6%)	4 (10.8%)	9 (9.0%)
Positive Urine Drug Screen at baseline for Fentanyl	42 (66.7%)	28 (75.7%)	70 (70.0%)
Unstable Housing [a] Past 12 Months	35 (55.6%)	13 (35.1%)	48 (48.0%)
Currently Living in Unstable Housing [a]	26 (41.3%)	10 (27.0%)	36 (36.0%)
# Days opioid used in the past 7-days (Mean (SD))	6.3 (1.57)	5.4 (2.03)	6.0 (1.79)
Route of Opioid Use			
Oral	5 (7.9%)	8 (21.6%)	13 (13.0%)
Nasal	25 (39.7%)	20 (54.1%)	45 (45.0%)
IV injection	26 (41.3%)	5 (13.5%)	31 (31.0%)

[a] Spent at least one night in: shelter for homeless; On the street/public place; welfare hotel; doubled up in someone else's house/apartment; emergency, temporary, transitional, or halfway house.

Summary of Primary Outcomes



COWS	Number Enrolled	≥ 5 increase in COWS within 4 hours of XR-BUP N (%, 95% CI)	Transition to moderate withdrawal within 4 hours of XR-BUP N (%, 95% CI)	Precipitated Withdrawal within 1-hour * of XR-BUP N (%, 95% CI)	Precipitated Withdrawal within 4 hours of XR-BUP* N (%, 95% CI)
4-7	63	4 (6.3%, 1.8 % - 15.5%)	2 (3.2%, 0.4% - 11.0%)	1 (1.6%, 0.04% - 8.5%)	**2 (3.2%,** 0.4% - 11.0%)
0-3	37	6 (16.2%, 6.2% 32.0%)	5 (13.5%, 4.5% -8.8%)	1 (2.7%, 0.1% - 14.2%)	**5 (13.5%,** 4.5% - 28.8%)

*** All cases were reviewed in detail and adjudicated by our expert consultants**

D'Onofrio et al. Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid Withdrawal, JAMA Netw Open, 2024

Daily Electronic Survey

Have you used opioids not prescribed for you in the last 24 hours?	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
No	75 (85%)	64 (80%)	65 (81%)	60 (79%)	59 (82%)	63 (80%)	59 (78%)
Yes	13 (14%)	16 (20%)	15 (18%)	16 (21%)	13 (18%)	16 (20%)	17 (22%)
Total Responses	88	80	80	76	72	79	76
VAS: Use the slider to indicate how much you desire opioids at this moment (0 - 100)							
Median (IQR)	15 (0-42)	10 (0-40)	10 (0-31)	10 (0-30)	10 (0-30)	10 (0-30)	10 (0-30)

D'Onofrio et al. Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid Withdrawal, JAMA Netw Open, 2024

Secondary Outcomes

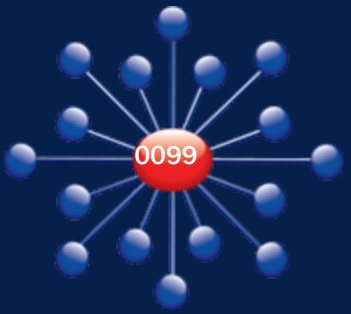
- **73% engaged in treatment on day 7**
  - Including 4/7 of those with PW
  - 0% confirmed not in treatment; 7% lost to follow-up

- On any given day among those who responded to daily follow-up survey:
  - Between 29-31 (33-43%) reported no opioid cravings
  - Between 59 – 75 (78-85%) reported no illicit opioid use
  - Over all 7 days of follow-up, 57 (60%) reported no illicit opioid use

- No episodes of opioid overdose reported in past 7 days (compared to 6 in past 7 days at baseline)

D'Onofrio et al. JAMA Netw Open, 2024

Conclusion



Treatment initiation with 7-day XR-BUP in ED patients with OUD and low levels of opioid withdrawal, defined as COWS of 4-7, is feasible, safe, well tolerated and addresses some of the oft-cited barriers to initiating care in the ED.

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ED-INitiated BupreNOrphine VAlidaTION Network Trial

To compare the effectiveness of XR-BUP and SL-BUP induction (8-12mg) in approximately 2000 patients with untreated OUD in the ED on the primary outcome of engagement in formal addiction treatment at 7 days

RCT
2,000
enrolled

D'Onofrio & Fiellin

June 2020 - August 2024

D'Onofrio, Contemporary Clinical Trials, 2021

Study Population

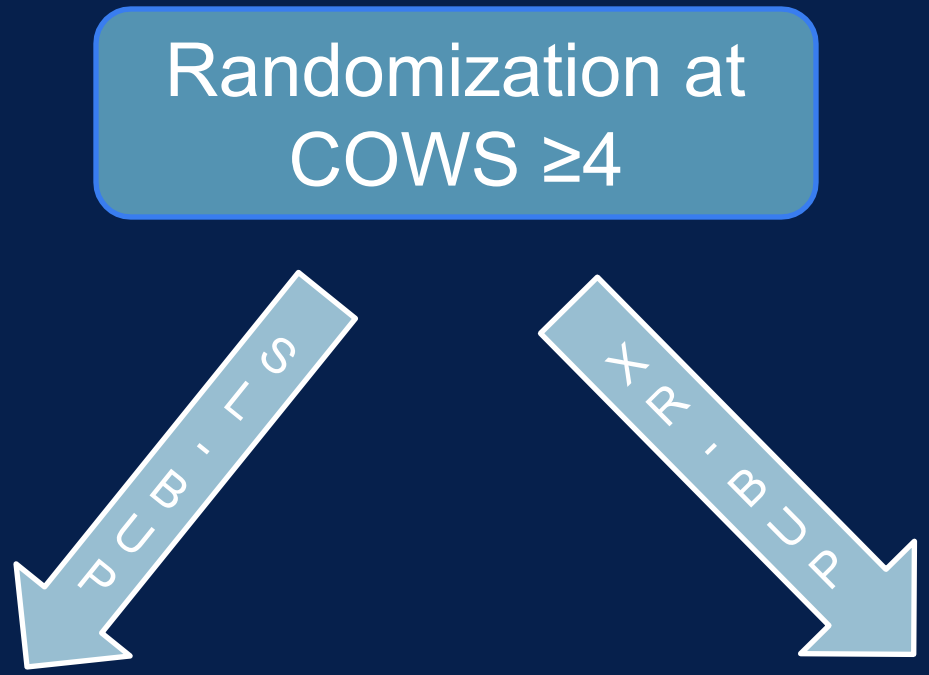
Inclusion Criteria

- DSM 5 Criteria for moderate/severe OUD
- 18 years or older in age
- Treated in the ED during screening hours
- COWS score ≥ 4 (modified in 2022)
- Urine toxicology test that is positive for opioids
- Speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study

Exclusion Criteria

- Urine positive for methadone
- Pregnancy
- Receiving MOUD treatment within past 7 days
- Medical/Psych condition requiring hospitalization
- Actively suicidal or cognitively impaired
- Require prescription for opioid analgesics
- A prisoner or in police custody

Study Schema



COWS 4-7

Unobserved SL Initiation

COWS ≥8

SL in ED

XR-BUP given in ED; Observed 2 hours

JAMA Network | Open™

Research Letter | Substance Use and Addiction

Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

Gail D'Onofrio, MD, MS; Kathryn F. Hawk, MD, MHS; Jeanmarie Perrone, MD; Sharon L. Walsh, PhD; Michelle R. Lofwall, MD; David A. Fiellin, MD; Andrew Herring, MD

Introduction

Buprenorphine treatment is associated with decreased mortality and morbidity,[1] yet the treatment gap remains wide. Emergency departments (EDs) offer an effective, low-barrier setting in which to initiate buprenorphine.[2] Retrospective case series[3] have raised concerns about increased incidence of precipitated withdrawal (PW) when buprenorphine is initiated in persons using fentanyl, a high-potency μ-opioid agonist with high affinity and slow dissociation from the μ receptor. With long-term use, its high lipophilicity leads to bioaccumulation and prolonged metabolite excretion. As confidence in standard buprenorphine inductions has eroded, alternative strategies, such as low-dose buprenorphine, have emerged, often prompting continued use of illicit opioids. Thus, there is a need for high-quality evidence from prospective studies using uniform surveillance and operational definitions of PW. We report the incidence of PW as part of an ongoing randomized clinical trial[4] comparing traditional sublingual buprenorphine with CAM2038, a 7-day extended-release injectable form of buprenorphine, conducted in sites with high prevalence of fentanyl.

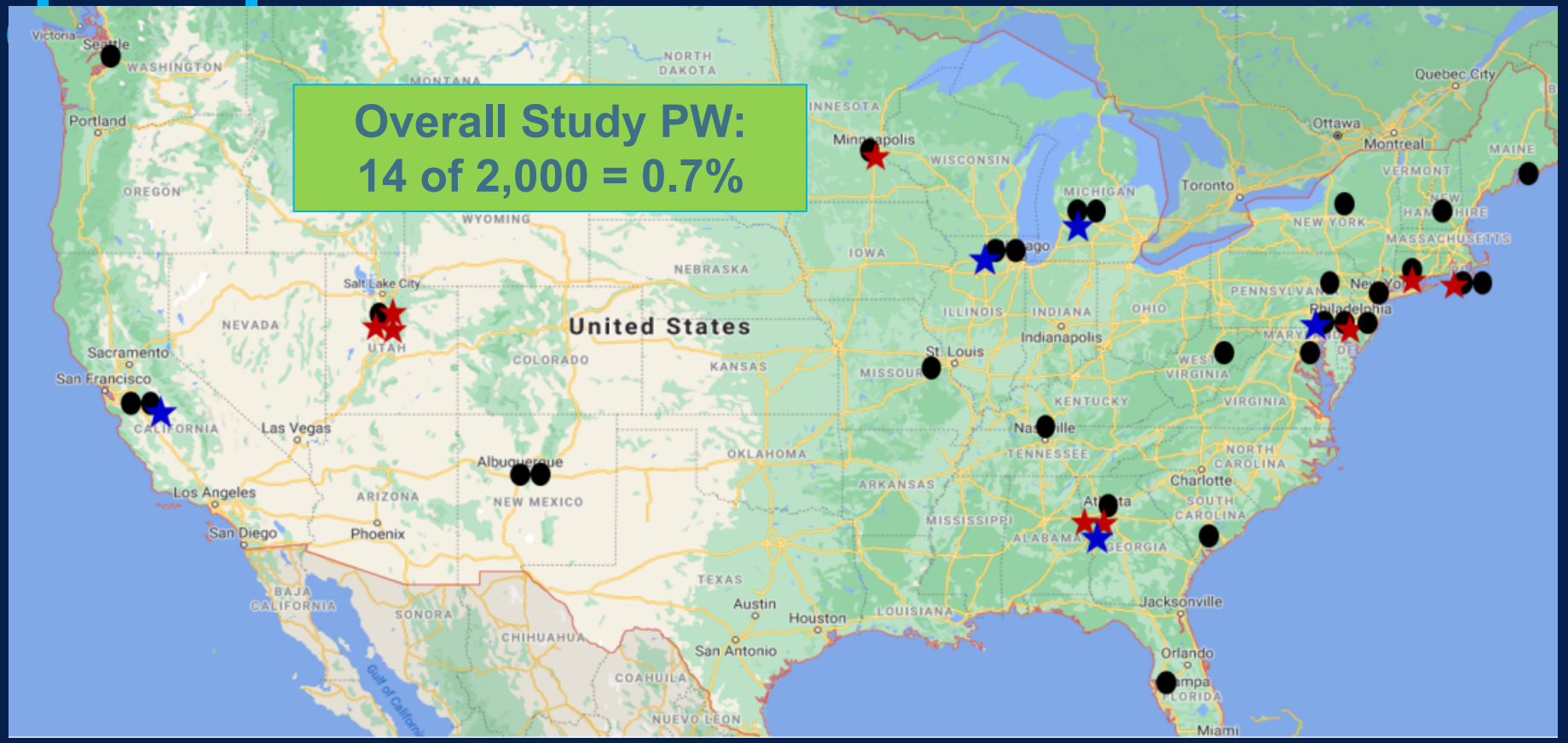
+ Supplemental content

Author affiliations and article information are listed at the end of this article.

9/1,200 = 0.76%

Buprenorphine induction in the ED remains safe and effective, even with fentanyl present

Location of all Enrolling Sites and Precipitated Withdrawal



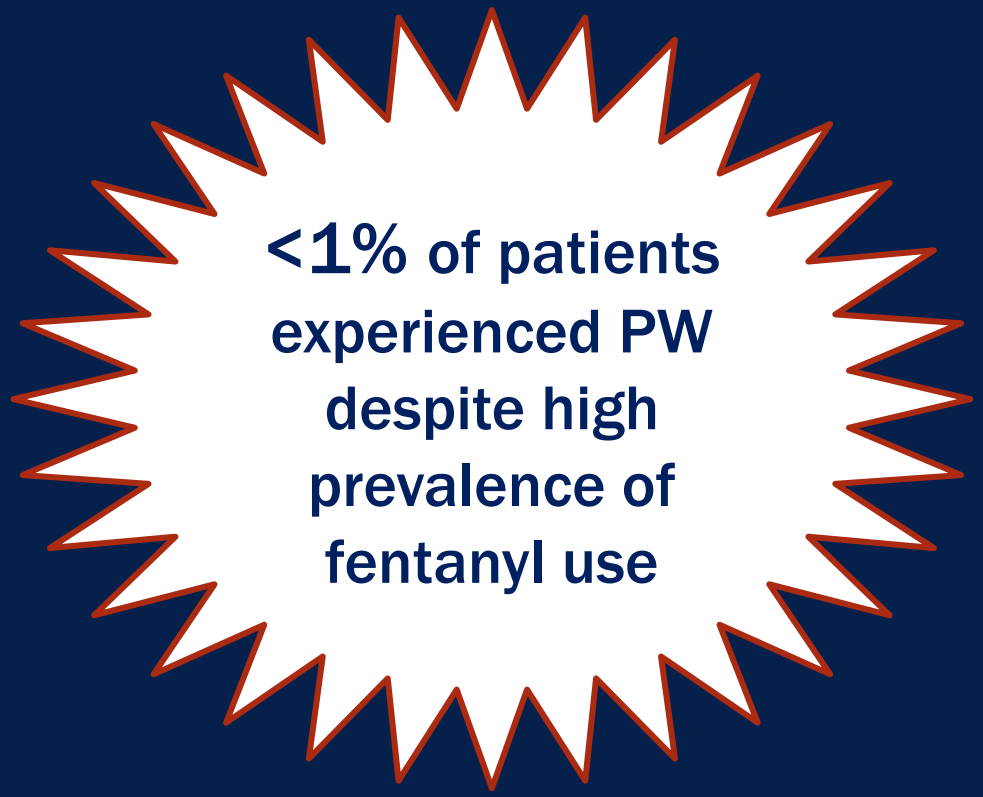
Key

Location of enrolling sites (29)
★ Location of SL-BUP precipitated withdrawal (9)
★ Location of XR-BUP precipitated withdrawal (5)

Enrollment by sites that experienced withdrawal

Site Location	# PW	Total enrolled	%
Northeast (11 sites)	4	476	**0.84**
West (6 sites)	4	619	**0.65**
Midwest (6 sites)	3	261	**1.1**
South (6 sites)	3	344	**0 .87**
Totals	**14**	**2,000**	**0.70**

Conclusion



There are NO consistent similarities among the individuals experiencing precipitated withdrawal

iStock

Lessons Learned: Treatment of PW

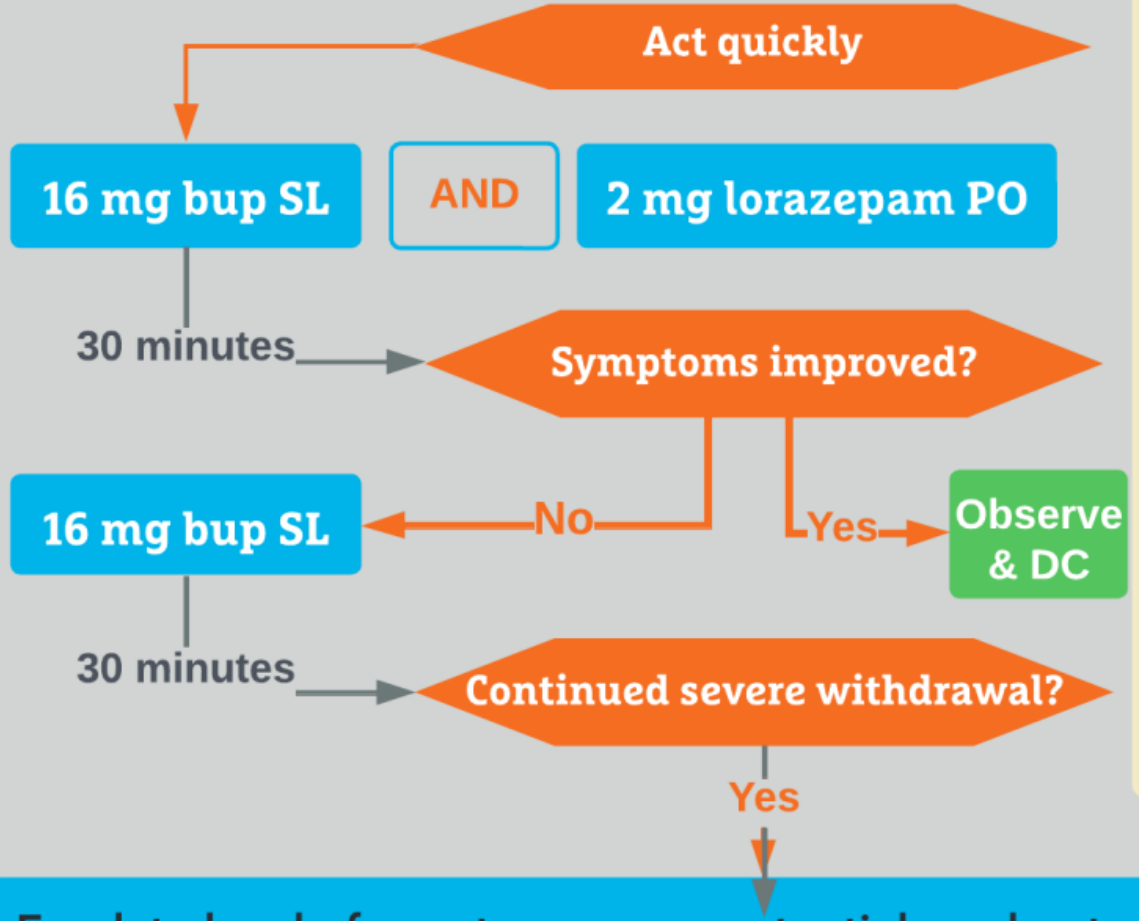
More Buprenorphine 24-32 mg!

- **Ancillary Medications**
  - Muscle aches and pains: Acetaminophen, NSAIDs: Ibuprofen, ketorolac
  - Abdominal cramps and diarrhea: Dicyclomine, Loperamide
  - Nausea: Antiemetics
  - Elevated blood pressure, tachycardia and/or anxiety/restlessness: Clonidine

- Consider IV Fluids & small doses of lorazepam
- Low threshold for Ketamine
- Best to find a dark quieter place or send home if possible

Treatment of bup precipitated withdrawal

(Sudden, significant worsening of withdrawal soon after bup administration)



Adjuvants:
OK but should not delay or replace bup. Use sparingly with appropriate caution.

Benzodiazepines:
- Lorazepam 2 mg PO/IV

Antipsychotics:
- Olanzapine 5 mg PO/IM

Alpha-agonists:
- Clonidine 0.1-0.3 mg PO

D2/D3 agonists:
- Pramipexole 0.25 mg PO

Gabapentinoids:
- Pregabalin 150 mg PO

Escalate level of care to manage potential moderate to deep sedation including cardiac, pulse oximetry, and end tidal CO2 monitoring:

1. Ketamine (0.3 mg/kg IV slow push q 15 minutes and/or infusion).
2. Fentanyl IV as needed

After clinical resolultion and observe and discharge with bup Rx and/or XR-Bup

BRIDGE

- Initiating buprenorphine in the ED is safe and effective
- 7-day injectable buprenorphine can be started in patients with COWS of 4 or more
- Precipitated withdrawal is rare and can be treated in the ED

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