Overview of the ED INNOVATION trial (CTN 0099) and Buprenorphine inductions in the ED in the age of Fentanyl

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ASAM National Conference, April 2024

Disclosure Information

Overview of the ED INNOVATION trial (CTN 0099) and Buprenorphine inductions in the ED in the age of Fentanyl

Kathryn Hawk, MD, MHS

April 6, 2024 at 10:30 am

- No Conflicts of Interest to Disclose

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 discuss the rationale behind ED INNOVATION, an ongoing RCT comparing the use of a 7-day injectable buprenorphine formulation to sublingual for treatment initiation in the ED.
- To describe how the use of a 7-day injectable buprenorphine formulation differs from sublingual.
- To discuss frequency of participated withdrawal among the first 1200 patients enrolled in ED INNOVATION and strategies for management in the ED setting.

We Know…

Treatment for OUD Works

Research Paper

Has the treatment gap for opioid use disorder narrowed in the U.S.?: A yearly assessment from 2010 to 2019”

Noa Krawczyk[a,*], Bianca D. Rivera[a], Victoria Jent[a], Katherine M. Keyes[b], Christopher M. Jones[c], Magdalena Cerdá[a]

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MOUD has increased over the past 10 years …
Only 13.4% of individuals with OUD received MOUD

Krawczyk N et al., International J Drug Policy 2022

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

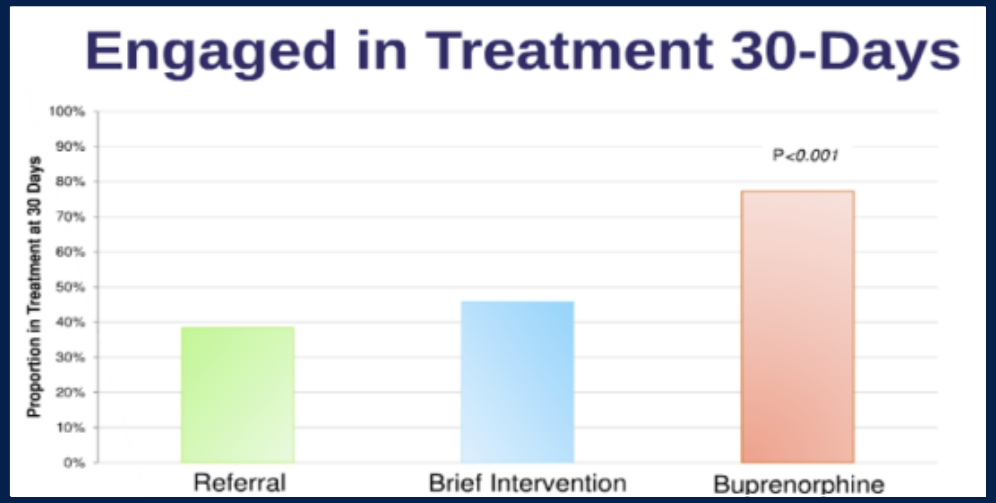
Preliminary Findings from Drug-Related Emergency Department Visits, 2021; SAMHSA/DAWN 2022

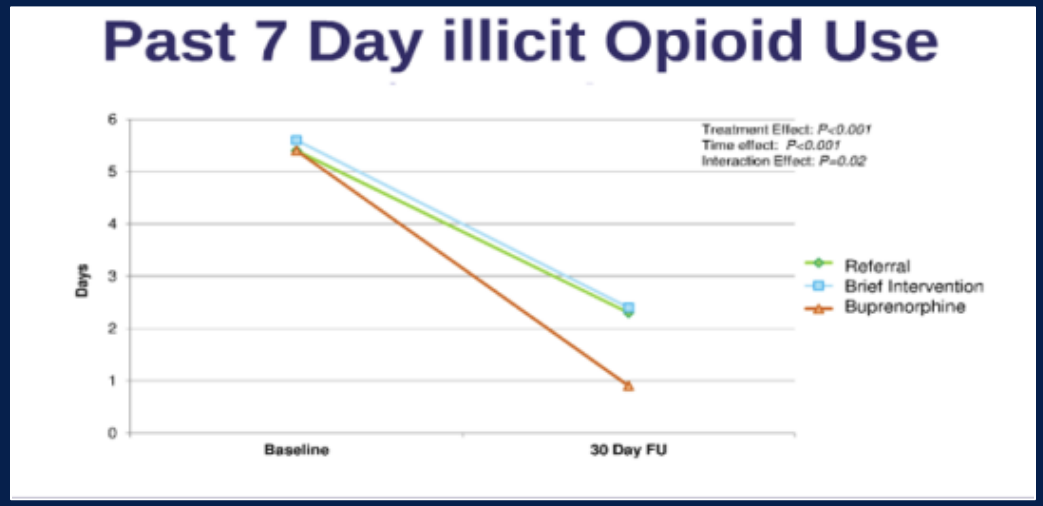
Research

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

Clinician Barriers to Treat

JAMA Network | Open

Hawk, JAMA Open, 2020

Original Investigation | Substance Use and Addiction

Barriers and Facilitators to Clinician Readiness to Provide Emergency Department–Initiated Buprenorphine

Barriers to implementation:

- Requirement for a X-waiver
- Lack of experience in treating OUD with buprenorphine
- Ability to link to treatment
- Competing priorities for ED time and resources,
- Misunderstanding and stigma toward patients with OUD

Solutions:

- Training
- Protocols integrated within the EHR
- Targeted feedback to ED staff on patient outcomes
- **ACEP Consensus Recommendations**

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

Strategies for ED Buprenorphine Initiation

- Standard ED Dosing
- High Dose
- Low 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

Injectable Formulations

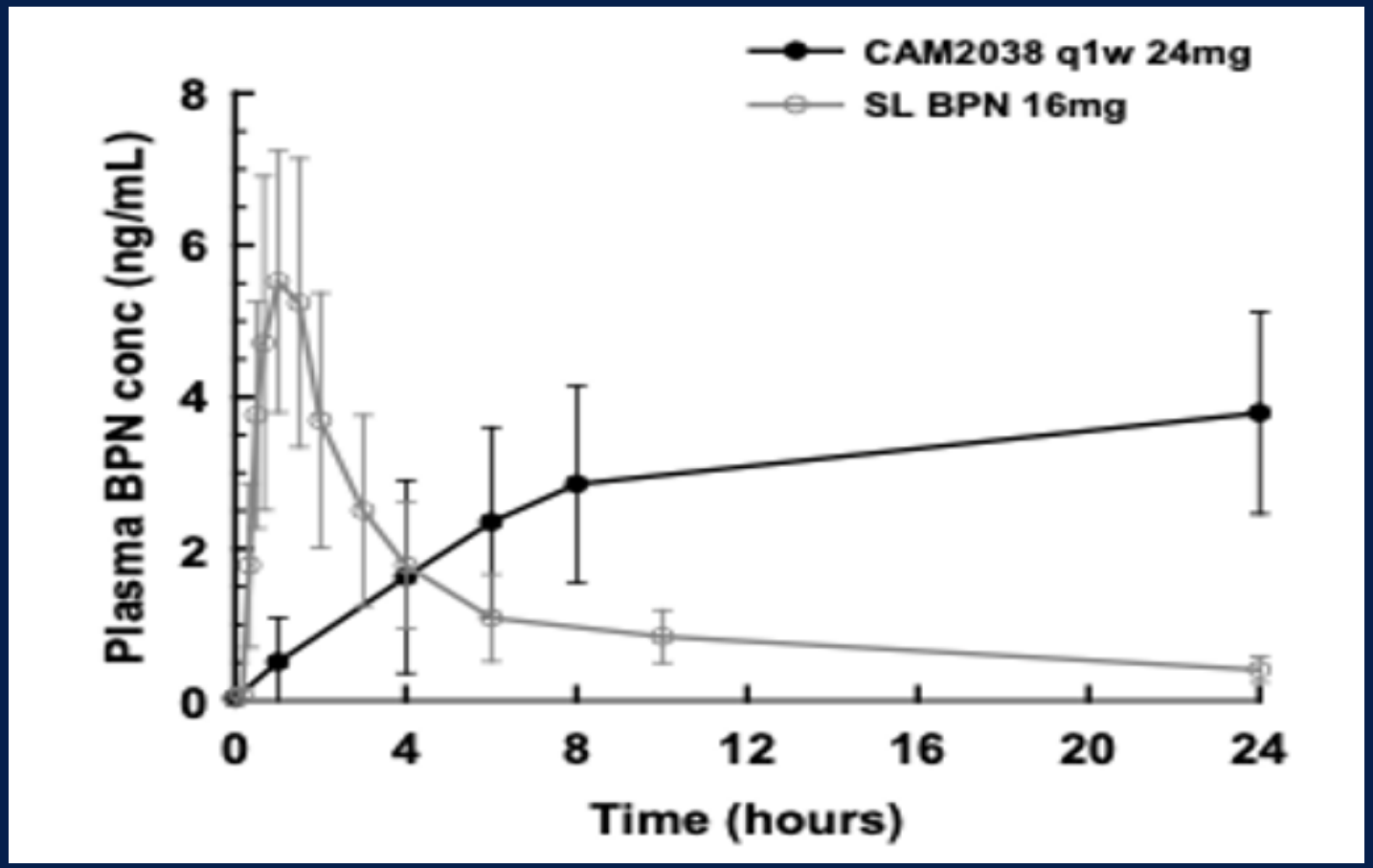
	Monthly buprenorphine injection	Weekly and monthly injection (CAM-2038)
Approval	Australia & USA	Australia, EMA, USA
Indications	Adults with moderate-severe OUD, tolerating SL bup at 8-24 mg/day for at least 7 days. Counseling and psychological support should be part of treatment plan.	Treatment OUD (age 16yrs +) within framework of medical, psychological and social treatment
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

ED INNOVATION

CAM2038 24mg XR-BUP 7-day injectable vs 16mg SL-BUP per day

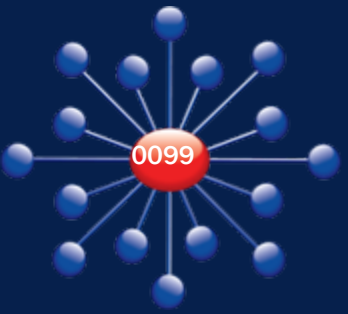
Pharmacokinetics of XR- & SL- Buprenorphine



Upon injection **CAM2038** forms into a viscous liquid crystalline gel, producing a sustained, non-fluctuating levels of buprenorphine in the blood **avoiding the peaks and troughs of daily dosing**

3UG1DA015831

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

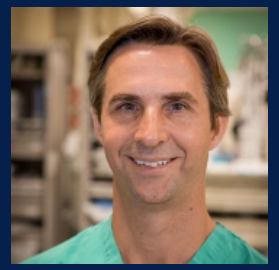
RCT
1872
enrolled

Lead Investigators

D'Onofrio, Contemporary Clinical Trials, 2021

Research Team





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Kristen Huntley PhD	Arjun Venkatesh, MD
Michelle R. Lofwall MD	Sharon Walsh, PhD
Shara Martel MPH, MS	









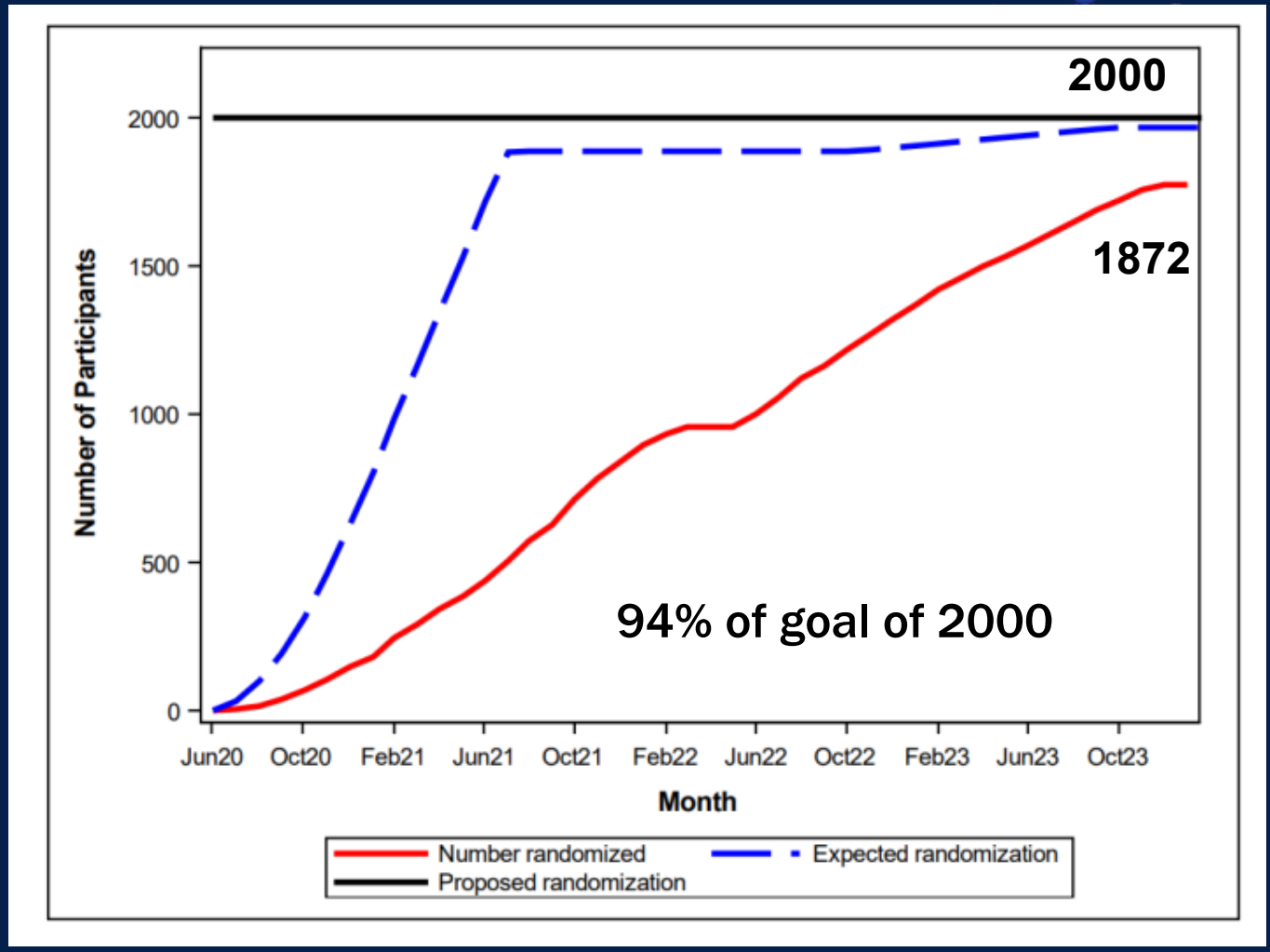


...and the ED Health, ED Connect & ED Innovation Core Investigators


Henry Ford Hospital
DMC Detroit Receiving Hospital
~~UChicago Medicine Hospital~~
Hennepin County Medical Center
Barnes-Jewish Hospital
~~Northwestern~~
Maine Medical Center
~~Dartmouth Hitchcock Medical Center~~
Rhode Island Hospital & The Miriam (6/2/2021) [2 sites/1 institution]
Yale New Haven Hospital
~~Upstate University Hospital~~
~~New York-Presbyterian Hospital~~
~~Temple University Hospital-Episcopal Campus~~
Penn Presbyterian Medical Center
University of Pittsburgh Medical Center
ED INNOVATION Sites
Initially: 28 Sites, 27 Institutions
United States
~~Johns Hopkins Hospital~~
Berkeley Medical Center
Harborview
San Leandro Hospital
Highland Hospital
University of Utah Hospital
University of New Mexico Hospital
~~Presbyterian Hospital (Albuquerque)~~
Medical University of South Carolina
Grady Memorial Hospital
Tampa General Hospital

Enrollment

Only 128 to go!!



2023												2024			
Jan	Feb	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec	JAN	FEB	MARCH	TOTAL
50	40	52	38	36	35	39	43	41	31	33	21	32	46	19	1872

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.

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.

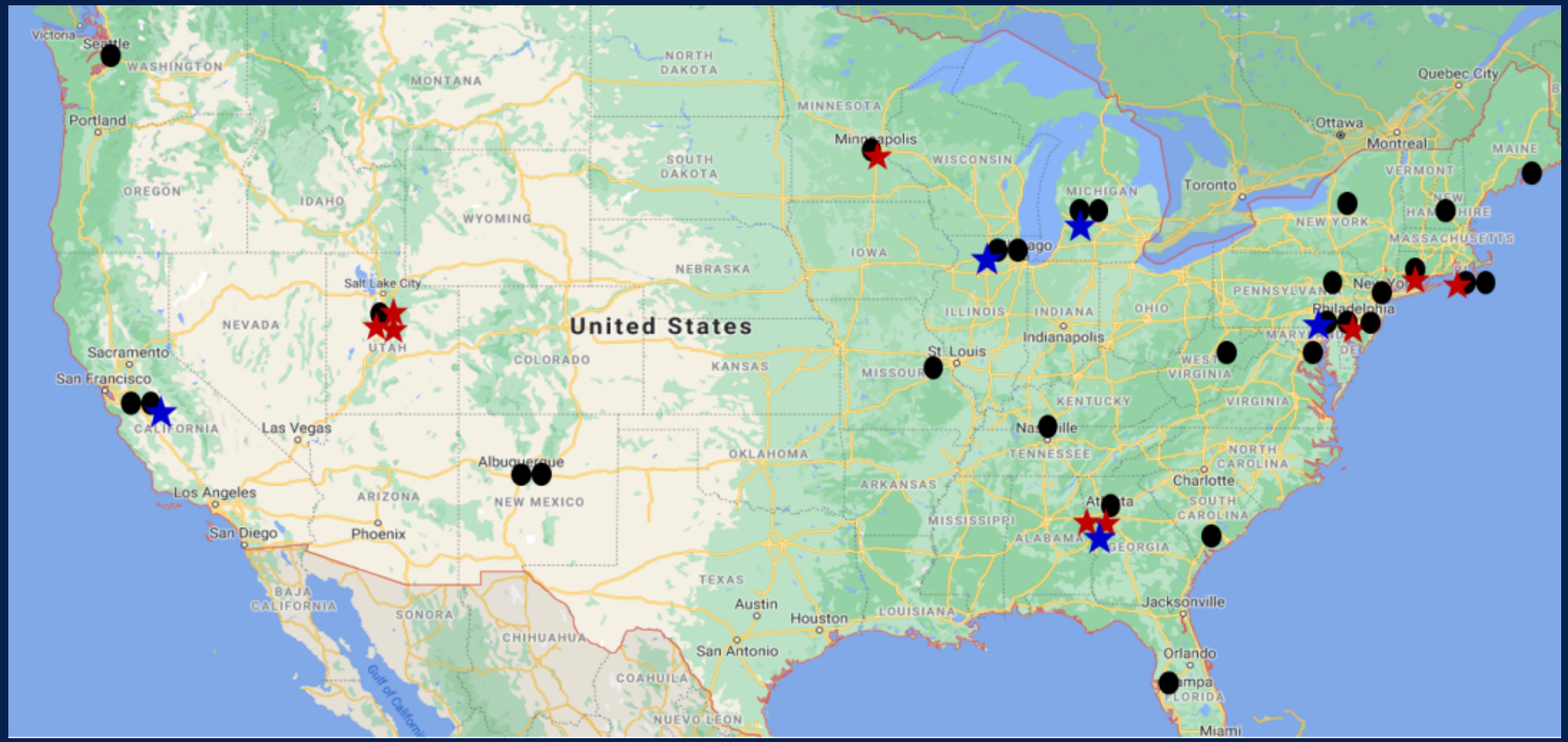
+ Supplemental content

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	.84
West (6 sites)	4	619	.65
Midwest (6 sites)	3	261	1.1
South (6 sites)	3	344	.87
Totals	**14**	**1700**	**.82**

Includes 9 cases between 06/2022 and 10/2022 and 5 from 10/22 to 10/2023.

A COWS increase of ≥ 5 are reviewed by our expert reviewers – Sharon Walsh PhD, Michele Lofwall MD

Results: Patient Characteristics

Total Enrolled to Date (n=1700)

- Male 68%
- Age (Mean) 38
- Race/Ethnicity: 55% White, 31% Black,
  2% Multiracial 2% American Indian
  15% Hispanic/Latino
- Urine Drug Screen (still need to update w/ new urine data)
  - 91% Multiple Drugs
  - 75% Fentanyl
  - 35% Cocaine
  - 46% Marijuana
  - 37% Opiates
  - 35% Methamphetamine

Patients with PW (n=14)

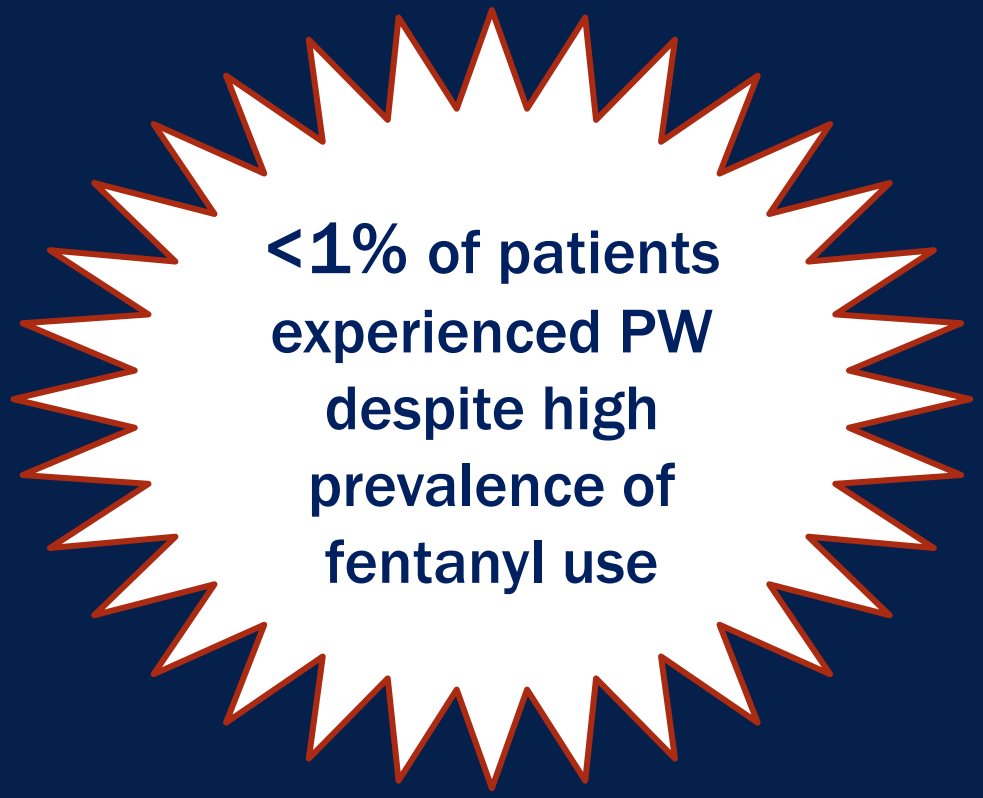
- Male 71%
- Age (Mean) 39
- Race/ Ethnicity: 5 (36%) White, 5 (36%) Black,
  2 (14%) Multiracial 1 (.7%) American Indian
  2 (14%) Hispanic/Latino
- Urine Drug Screen
  - 86% Multiple Drugs
  - 100% Fentanyl
  - 57% Cocaine
  - 36% Marijuana
  - 29% Opiates
  - 14% Methamphetamine

Characteristics of Patients with Precipitated Withdrawal

Enrollment Date	Location	Age	Race	Hispanic Y/N	Gender	Severity of Use Days/wk	Last Use (hours)	Route	Baseline COWS	Urine Drug Testing	BUP SL vs XR	Disposition	ED LOS (hours/min)
12/20	Northeast	50	Black	n	Woman	7	16	IV	13	OPI FEN	SL	Discharged	6.40
01/21	West	29	White	n	Woman	7	8	smoking	15	FEN	XR	Discharged	2.50
02/21	Northeast	47	White	n	Man	7	8	nasal	12	FEN	XR	Observation[a] Discharged	7.50
04/21	Midwest	61	Black	n	Woman	7	24	nasal	8	COC, OPI, THC, FEN	XR	AMA	1.41
05/21	Northeast	30	Muti-racial	n	Man	6	>24	IV	17	COC, THC, FEN	SL	Discharged	7.24
8/21	South	32	Multi-racial	y	Man	6	24	smoking	16	COC, FEN	SL	Observation[a] Discharged	22.39
9/21	Midwest	49	Black	n	Man	7	12	nasal	13	COC, THC, FEN	XR	Discharged	8.50
11/21	Midwest	22	AI/AN	n	Man	7	16	smoking	10	COC, THC, FEN	SL	Discharged	8.43
12/21	South	25	black	n	Man	7	15	IV	29	COC, FEN	SL	Observation[a] Discharged	20.00
4/23	Northeast	31	white	n	Man	7	9	nasal	7	COC, OPI, FEN	SL	Observation[a] Discharged	19.22
6/23	West	31	white	n	Woman	7	24	smoking	18	AMP, MET, OPI, FEN	SL	Discharged	6.25
7/23	West	33	declined	y	Man	6	16	smoking	10	AMP, THC, FEN	SL	Discharged	4.46
8/23	West	58	White	n	Man	7	17	smoking	8	OPI, FEN	SL	Admitted/ AMA	7.49
9/23	South	52	black	n	Man	6	>24	nasal	5	BUP, COC, MET OPI, FEN	XR	Discharged	5.57

[a] Placed In ED observation status and then discharged

Conclusion



There are NO consistent similarities among the individuals experiencing Precipitated Withdrawal!

Lessons Learned: Treatment of PW

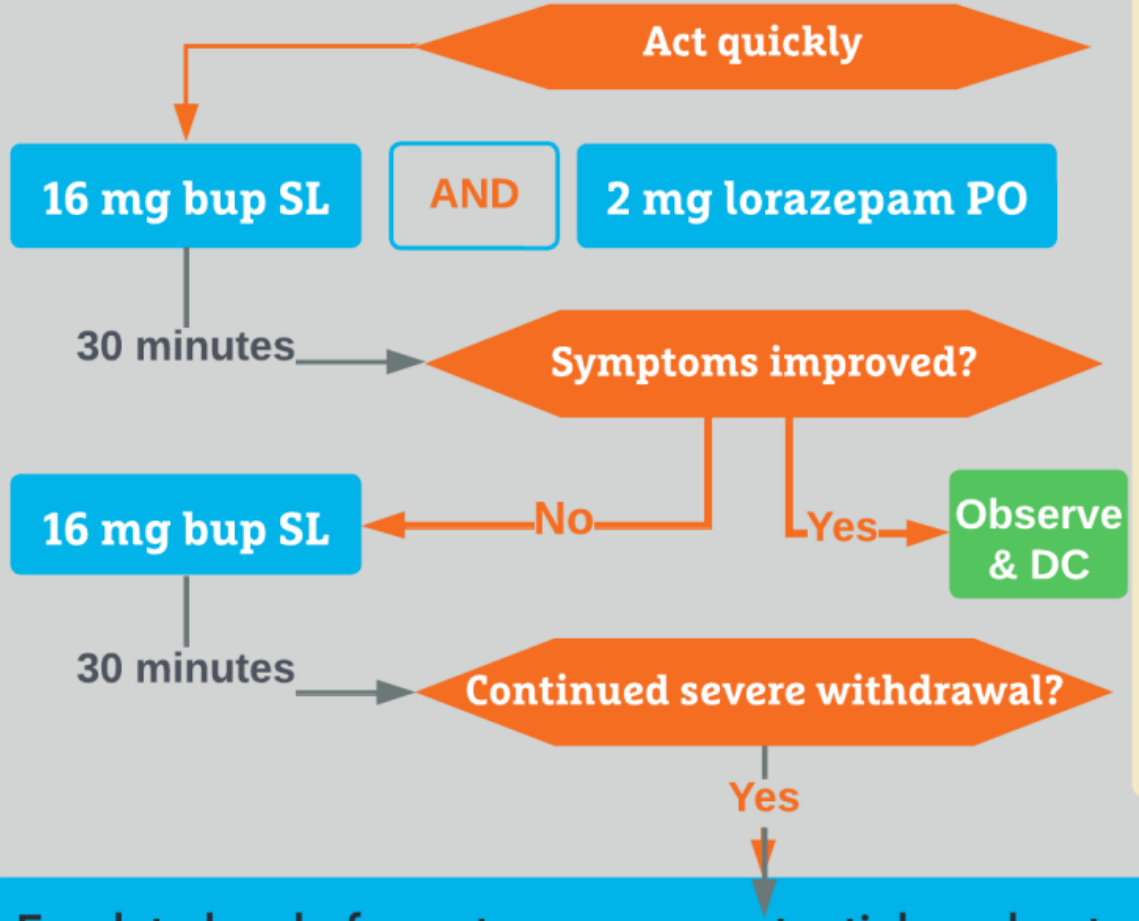
More Buprenorphine 24-32 mg!

- **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

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